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L2 and (tyrosine$ with substitution$)	0

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L3	L2 and aggregans	0	L3
L2	L1 and pcr	1	L2
L1	6008025.pn.	2	L1

END OF SEARCH HISTORY

POLYMERASE AND TYROSINE

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S4	35	RD (unique items)

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4/3,K/1 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2004 Inst for Sci Info. All rts. reserv.

04991841 Genuine Article#: UX738 No. References: 44
Title: DOMAIN ORGANIZATION AND DNA-INDUCED CONFORMATIONAL-CHANGES OF AN ARCHAEAL FAMILY-B DNA-*POLYMERASE*
Author(s): PISANI FM; MANCO G; CARRATORE V; ROSSI M
Corporate Source: CNR,IST BIOCHIM PROT ENZIMOL,VIA G MARCONI 10/I-80125 NAPLES//ITALY/
Journal: BIOCHEMISTRY, 1996, V35, N28 (JUL 16), P9158-9166
ISSN: 0006-2960
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

Title: DOMAIN ORGANIZATION AND DNA-INDUCED CONFORMATIONAL-CHANGES OF AN ARCHAEAL FAMILY-B DNA-*POLYMERASE*
Abstract: Family B DNA *polymerase* from the thermoacidophilic archaeon Sulfolobus solfataricus (Sso DNA pol) is a monomer of about 100 kDa with two associated catalytic functions: 3'-5' exonuclease and DNA *polymerase* activities. The structure of this enzyme in the free and DNA-bound states was probed by limited proteolysis and fluorescence spectroscopy measurements. The results of...

...It was found to start at residues 392-394 and to span the protease-hypersensitive central region of the polypeptide chain. Its involvement in critical *polymerase* functions, such as substrate binding and/or enzyme processivity, was discussed. In addition, we found that controlled trypsin digestion of Sso DNA pol did nor inactivate either *polymerase* or 3'-5' exonuclease activity concomitantly with the disappearance of full-sized enzyme. Activity gel analysis revealed that proteolytic products corresponding to the amino- and carboxyl-terminal halves of the enzyme retained 3'-5' exonuclease and DNA *polymerase* activity, respectively. These results are in line with the model of modular organization proposed for Sso DNA pol in a previous report [Pisani & *Rossi* (1994) J. Biol. Chem. 269, 7887-7892].
...Research Fronts: COLI PRIMARY REPLICATIVE HELICASE DNAB PROTEIN; LOCAL CONFORMATIONAL-CHANGES)
94-8153 001 (RECOMBINANT GENES IN ESCHERICHIA-COLI; PROTEIN-PROTEIN INTERACTIONS; DNA-BINDING DOMAINS; PACA SUBUNIT; *TYROSINE* PHOSPHORYLATION)

4/3,K/2 (Item 1 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text
(c) 2004 The HW Wilson Co. All rts. reserv.

04755408 H.W. WILSON RECORD NUMBER: BGSA02005408 (USE FORMAT 7 FOR FULLTEXT)
Mechanisms of iron accumulation in hereditary hemochromatosis.
Fleming, Robert E
Sly, William S
Annual Review of Physiology v. 64 (2002) p. 663-80
SPECIAL FEATURES: bibl il ISSN: 0066-4278
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 9204

(USE FORMAT 7 FOR FULLTEXT)

TEXT:
... 2; see color insert). The mutation found to be associated with HH was a single base change in exon 4, resulting in the substitution of *tyrosine* for cysteine at amino acid 282 of the deduced amino acid sequence of the unprocessed protein (C282Y). This corresponds to amino acid 260 of the...

...C282Y
The majority of patients with classical HH have a single base change in exon 4 of the HFE gene, leading to the substitution of *tyrosine* for cysteine at amino acid 282 of the unprocessed protein (C282Y). This mutation was also proven to cause murine HH when knockin of the C282Y...
Beckman L. 1997. Ethnic differences in the HFE codon 282 (Cys/Tyr) polymorphism. Hum. Hered. 47:263-67
60. Olynyk JK, Cullen DJ, Aquilia S, *Rossi* E, Summerville L, Powell LW. 1999. A population-based study of the clinical expression of the hemochromatosis gene. N. Engl. J. Med. 341:718-24
61. Chang JG, Liu TC, Lin SF. 1997. Rapid diagnosis of the HLA-H gene Cys 282 Tyr mutation in hemochromatosis by *polymerase* chain reaction-a very rare mutation in the Chinese population. Blood 89:3492-93
62. Cullen LM, Gao X, Easteal S, Jazwinska EC. 1998. The...

4/3,K/3 (Item 2 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

04750841 H.W. WILSON RECORD NUMBER: BGSA02000841 (USE FORMAT 7 FOR FULLTEXT)
Sub-Saharan genetic contribution in Morocco: microsatellite DNA analysis.
Dios, S
Luis, J. R; Carril, J. C
Human Biology (Hum Biol) v. 73 no5 (Oct. 2001) p. 675-88
SPECIAL FEATURES: bibl graph map tab ISSN: 0018-7143
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 5244

(USE FORMAT 7 FOR FULLTEXT)

TEXT:
... The main goal of this paper is to assess these phenomena through the analysis of four STR (short tandem repeat) DNA markers by means of *polymerase* chain reaction (PCR) (Saiki et al. 1985) corresponding to intronic regions (Litt and Luty 1989; Weber and May 1989). These genetic markers are of particular...

...population of northern Morocco. The geographical districts of the origin of individuals are Titt' Aoouen, Fes, Al Hoseima, Taza, Nador, and Oudjda regions (Figure 1).
Polymerase Chain Reaction. PCR amplification for TPOX, VWA, and TH01 was as previously detailed (Dios et al. 1998). For the F13B locus, PCR was performed in...

...pH 8.4, 50 mM KCl buffer, 20-100 ng of DNA, 200 mM each deoxynucleotide, 1 mM each primer, 0.5 U Taq DNA *polymerase* (Gibco-BRL), and 3 mM MgCl2. The optimized conditions were: denaturing at 96[degree]C for 1 min, followed by annealing at 60[degree]C...M., E.S. Berg, and B. Olaisen. 1994. Four STRs in 300 Norwegians. In Advances in Forensic Haemogenetics 5, W. Bar, A. Fiori, and U. *Rossi*, eds. Berlin and Heidelberg, Germany, 539-541.

Dutour, O., R. Vernet, and G. Aumassip. 1988. Le peuplement prehistorique du Sahara. In Milieux, hommes et techniques...of Portugal. J. Forensic Sci. 42:121-124.

Polymeropoulos, M.H., H. Xiao, D.S. Rath et al. 1991. Tetranucleotide repeat polymorphism at the human *tyrosine* hidroxilase gene (TH). Nucleic Acids Res. 19:37-53.

Prata, M.J., A. Amorim, L. Gusmao et al. 1996. Population genetics of the STRs TPO...Legal Med. 111:105-106.

Weber, J.L., and P.E. May. 1989. Abundant class of human DNA polymorphisms which can be typed using the *polymerase* chain reaction. Am. J. Hum. Genet. 44:388-396.

Woller, J., S. Furedi, and Z. Padar. 1996. Hungarian population data for 11 PCR-based polymorphisms...

4/3,K/4 (Item 3 from file: 98)

04512172 H.W. WILSON RECORD NUMBER: BGSA01012172 (USE FORMAT 7 FOR FULLTEXT)

DNA topoisomerases: structure, function, and mechanism.

Champoux, James J
Annual Review of Biochemistry v. 70 (2001) p. 369-413
SPECIAL FEATURES: bibl il ISSN: 0066-4154
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 19323

(USE FORMAT 7 FOR FULLTEXT)

...ABSTRACT: the enzymes. The type IB enzymes are structurally distinct from all other known topoisomerases but are similar to a class of enzymes referred to as *tyrosine* recombinases. The structural themes common to all topoisomerases include hinged clamps that open and close to bind DNA, the presence of DNA binding cavities for...

TEXT:

... the cell (1). Thus, during DNA replication, the two strands of the DNA must become completely unlinked by topoisomerases, and during transcription, the translocating RNA *polymerase* generates supercoiling tension in the DNA that must be relaxed (1, 2). The association of DNA with histones and other proteins introduces supercoiling that requires...

...for the background literature (16).

CLASSIFICATION OF TOPOISOMERASES

DNA cleavage by all topoisomerases is accompanied by the formation of a transient phosphodiester bond between a *tyrosine* residue in the protein and one of the ends of the broken strand. DNA topology can be modified during the lifetime of the covalent intermediate...case it has been shown that a specific substrate for the plasmid-encoded topoisomerase is generated during the initiation of plasmid DNA replication by DNA *polymerase* I (25).

CELLULAR ROLES OF TOPOISOMERASES

As a backdrop to the discussion to follow, the cellular roles of the various topoisomerases are reviewed, especially as...
...of replication and for transcription from at least some promoters (32). Transcription itself generates positive supercoils ahead of and negative

supercoils behind the translocating RNA *polymerase* that are rapidly resolved by DNA gyrase and DNA topoisomerase I, respectively.

Fork movement during replication of a circular DNA can generate topological changes in...DNA strand is accompanied by covalent attachment of one of the DNA ends to the enzyme through a 5' phosphodiester bond to the active site *tyrosine*. (c) All require Mg(II) for the DNA relaxation activity. (d) Plasmids containing negative, but not positive, supercoils are substrates for the relaxation reaction. (e...

...divided into three domains (Figure 1). The first 582 N-terminal amino acids correspond to a core "cleavage/strand passage" domain containing the active site *tyrosine* at position 319. Expression of a 596 amino acid N-terminal fragment of E. coli topoisomerase I yields a protein that retains the ability to...that as the single-stranded DNA binds to the cleft, domain III undergoes a conformational adjustment to place the nucleophilic O-4 oxygen of the *tyrosine* side chain in position to attack the scissile phosphate. After cleavage, the active site Tyr319 is covalently bound to the 5' phosphate on one end...of a Mg(II) requirement for cleavage and probably also for religation (94). Although mutation of a number of other residues near the active site *tyrosine* to alanines had little effect on the cleavage reaction, changing Glu9 to alanine abolished cleavage whereas a change to glutamine at this position had little...

...oxygen atom of the Tyr319 hydroxyl. This observation led to the suggestion that the positively charged arginine side chain might promote nucleophilic attack of the *tyrosine* O-4 atom on the scissile phosphate by stabilizing the phenolate anion. An earlier finding that Arg321 can be replaced by lysine, but only poorly...

...parallel those found in topoisomerase I. Most notably, the structures are very similar within the CAP region of domain III that contains the active site *tyrosine* residues and surrounding amino acids. The cleft where the single-stranded substrate has been proposed to bind appears a little deeper and better defined in...the third enzyme on the list, it is not considered further here. As is discussed below, these topoisomerases share structural and functional properties with the *tyrosine* recombinases that include the bacteriophage P1 Cre, and E. coli XerD recombinases, and certain phage integrases (108).

The members of the type IB subfamily of...
...no requirement that the substrate DNA be at least partially single-stranded. The type IB topoisomerases form a covalent intermediate in which the active site *tyrosine* becomes attached to the 3' phosphate end of the cleaved strand rather than the 5' phosphate end found for the type IA enzymes. The enzymes...

...N-terminal domain is followed by a highly conserved, 421 amino acid core domain that contains all of the catalytic residues except the active site *tyrosine* (125). A protease-sensitive and poorly conserved linker domain comprising 77 amino acids connects the core domain to the 53 amino acid C-terminal domain...

...in the structure. Although it was necessary to inactivate the enzyme by replacing the active site Tyr723 with phenylalanine to obtain crystals, by modeling a *tyrosine* in place of the phenylalanine in the structure, it can be seen that the *tyrosine* side chain is buried between core subdomain III and the C-terminal domain and is close to the scissile ...sequence homology, most of core subdomain III of human topoisomerase I (residues 440-614) superimposes structurally on the catalytic core region of a family of *tyrosine* recombinases that includes bacteriophages HPI and l integrases, and E. coli XerD and bacteriophage P1 Cre recombinases (125, 130-133). In addition, a region near...
...covalent intermediate involving attachment of the enzyme to the 3' phosphate of the cleaved strand. Most strikingly, the architecture of the active sites for the *tyrosine* recombinases are very similar to what is found for human topoisomerase I (see below) (108, 125). Thus, the

tyrosine recombinases and type IB topoisomerases possess functional cores that use the same chemistry to carry out cleavage and religation. The two classes of enzymes are...

...I prefers supercoiled over relaxed plasmid DNAs as substrates (138, 139), and the use of a mutant form of the protein with phenylalanine instead of *tyrosine* at the active site (Y723F) showed that the enzyme has a strong preference for binding to supercoiled DNA over relaxed DNA (140). This binding property...

...Catalysis Nucleophilic attack by the O-4 oxygen of Tyr723 on the scissile phosphate breaks the DNA strand to generate a phosphodiester link between the *tyrosine* and the 3' phosphate, releasing a 5' hydroxyl. Two different orientations of key active site residues in relation to the scissile phosphate were observed in...could be activated by the proximity of a general base (89, 108, 143), none of the structures revealed an amino acid close enough to the *tyrosine* to play this role. However, a water molecule has been found hydrogen-bonded to Arg590 that is only 2.3 A from the O-4...

...some conditions (149, 150). Similar results have been reported for the vaccinia topoisomerase where there is also the suggestion that after mutating the active site *tyrosine* to histidine or glutamine, water may be able to participate in the cleavage reaction (146, 151, 152). These results indicate that the key to catalysis...The recognition site specificity and the observation that the vaccinia enzyme can resolve Holliday junctions (154, 155) indicate an overlap in function with the related *tyrosine* recombinases and suggest that the viral topoisomerase may have multiple functions during the infection.

Structurally, vaccinia topoisomerase appears to be a pared-down cellular topoisomerase...

...encompassing the active site of human topoisomerase I. This region of similarity is the same as that found between the human topoisomerase I and the *tyrosine* recombinases. When the vaccinia and human enzymes are superimposed, all of the active site residues align very well except for a significant displacement of the active site *tyrosine* in the vaccinia structure compared to the human enzyme (128). This displacement, which was also observed for the l integrase and the XerD recombinase, suggests... ...163). (f) As with the type I enzymes, a highly conserved arginine residue is implicated in catalysis by its close proximity to the active site *tyrosine* (83, 166).

Several characteristics distinguish individual members of the type II family. All of the type II enzymes from both prokaryotic domains of life described...in orange and green, respectively. In panel a, the amino terminus (N) and carboxyl terminus (C) of the protein are indicated, and the active site *tyrosine* is shown in black ball and stick. The long a-helix that connects the cap to the base of the core is labeled "Connector" in...Crisona NJ, Hirano T, Cozzarelli NR. 1999. Cell 98:239-48

61. Chen M, Beck WT. 1995. Oncol. Res. 7:103-11

62. Dereuddre S, *Frey* S, Delaporte C, Jacquemin-Sablon A. 1995. Biochim. Biophys. Acta 1264:178-82

63. Yang X, Li W, Prescott ED, Burden SJ, Wang JC. 2000...Res. 58:2091-94

115. Gobert C, Skladanowski A. Larsen AK. 1999. Proc. Natl. Acad. Sci. USA 96:10355-60

116. Gobert C, Bracco L, *Rossi* F, Olivier M, Tazi J, et al. 1996. Biochemistry 35:5778-86

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4/3,K/5 (Item 4 from file: 98)

04508071 H.W. WILSON RECORD NUMBER: BGSA01008071 (USE FORMAT 7 FOR FULLTEXT)

Cytoplasmic signaling pathways that regulate cardiac hypertrophy.

Molkentin, Jeffery D
Dorn, Gerald W

Annual Review of Physiology v. 63 (2001) p. 391-426
SPECIAL FEATURES: bibl il ISSN: 0066-4278
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 15255

(USE FORMAT 7 FOR FULLTEXT)

TEXT:

... II) are peptides that convey growth-factor-like signals which promote cellular proliferation and/or differentiation through binding to a specific heterotetrameric receptor with intrinsic *tyrosine* kinase activity (reviewed in 174). The activated IGF receptor phosphorylates the insulin receptor substrates (IRSs) 1 and 2 (IRS-1 and IRS-2) leading to...

...within the heart, acting as autocrine or paracrine growth factors (reviewed in 189). FGF-2 and TGFb each bind separate membrane receptors that have intracellular *tyrosine* kinase activity (FGF) or serine-threonine kinase activity (TGFb) to elicit further signaling.

In adult cardiac myocytes, pacing induced FGF-2 release from cardiomyocytes, which...hearts (200), and overexpression of activated Src in neonatal cardiomyocytes induced hypertrophy through a Ras- and Raf-dependent pathway (201). Focal adhesion kinase another nonreceptor *tyrosine* kinase, was also reported to induce cardiac hypertrophy when overexpressed in transgenic mouse hearts (202). Neuregulin signaling through the ErbB2 or ErbB4 receptors (member of...

...pressure overload, suggesting that lowered ErbB receptor signaling plays a role in loss of hypertrophy and decompensation (204). Signaling through the epidermal-growth-factor-like *tyrosine* kinase receptor can also induce cardiomyocyte hypertrophy in culture (205).

A number of other less typical signaling pathways may also play a role in cardiac...

...PI3K, phosphatidylinositol 3-kinase; IP3, inositol 3-phosphate; DAG, diacylglycerol.

Figure 2 Ras signaling pathways. Ras is activated through G protein-coupled receptors (GPCR), receptor *tyrosine* kinases (RTK), Janus kinase 1 (Jak), or increases in intracellular calcium resulting in GDP-GTP exchange and the activation of numerous effector proteins. Abbreviations: PKC...

...activating protein.

Figure 3 Mitogen-activated protein kinase signaling pathways (MAPK). MAPK signaling pathways are activated in cardiomyocytes by G protein-coupled receptors (GPCRs), receptor *tyrosine* kinases (RTKs), transforming growth factor b receptor (TGFR), protein kinase C (PKC), calcium, or stress stimuli. These upstream events result in the activation of mitogen...AM, Bristow MR. 1991. Al-adenosine receptor inhibition of adenylate cyclase in failing and nonfailing human ventricular myocardium. Circulation 83:1343-51

13. Marzo KP, *Frey* MJ, Wilson JR, Liang BT, Manning DR, et al. 1991. Beta-adrenergic receptor-G protein-adenylate cyclase complex in experimental canine congestive heart failure produced...46. Adams JW, Sah VP, Henderson SA, Brown JH. 1998. Prostaglandin F2a-stimulated hypertrophic growth in neonatal rat cardiac myocytes is mediated by action of *tyrosine* kinases and Jun N-terminal kinase. Circ. Res. 83:167-78

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67. Abdellatif M, Packer SE, Michael LH, Zhang D, Charng MJ, Schneider MD. 1998. A Ras-dependent pathway regulates RNA *polymerase* II phosphorylation in cardiac myocytes: implications for cardiac hypertrophy. Mol. Cell. Biol. 11:6729-36

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...J. Biol. Chem. 271:8452-57

81. Zou Y, Komuro I, Yamazaki T, Aikawa R, Kudoh S, et al. 1996. Protein kinase C, but not *tyrosine* kinases or Ras, plays a critical role in angiotensin II-induced activation of Raf-1 kinase and extracellular signal-regulated protein kinases in cardiac myocytes...IL-6 beta receptor components. Science 263:92-95

159. Zhong Z, Wen Z, Darnell JE Jr. 1994. Stat3: a STAT family member activated by *tyrosine* phosphorylation in response to epidermal growth factor and interleukin-6. Science 264:95-98

160. Nakafuku M, Satoh T, Kaziro Y. 1992. Differentiation factors, including...

4/3,K/6 (Item 5 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

04501759 H.W. WILSON RECORD NUMBER: BGSA01001759 (USE FORMAT 7 FOR FULLTEXT)
Evolutionary origin of feathers.
AUGMENTED TITLE: symposium
American Zoologist (Am Zool) v. 40 no4 (Sept. 2000) p. 455-706
ISSN: 0003-1569
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 158028

(USE FORMAT 7 FOR FULLTEXT)

TEXT:
... b; Whitbread et al., 1991). We used the known feather b keratin sequences described in Presland et al. (1989a) to design primers for the polymerase *chain* reaction (PCR) to amplify the DNA sequences of feather b keratins from different birds. These primers amplify feather b keratins from a variety of avian...

4/3,K/7 (Item 6 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

04274002 H.W. WILSON RECORD NUMBER: BGSA00024002 (USE FORMAT 7 FOR FULLTEXT)
Pathogenicity islands and the evolution of microbes.
Hacker, Jorg
Kaper, James B
Annual Review of Microbiology v. 54 (2000) p. 641-79
SPECIAL FEATURES: bibl diag tab ISSN: 0066-4227
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 17927

(USE FORMAT 7 FOR FULLTEXT)

TEXT:
... 16, 48). This region encodes a type III secretion system that translocates a number of effector proteins into host cells. The YopH protein has a *tyrosine* phosphatase activity, and it inhibits phagocytosis and disrupts focal adhesions of HeLa cells. The YopE protein, for which no enzymatic activity has been described, also...DR sequences that resemble phage att sites (56). Culture supernatants of VPI-positive V. cholerae

strains contained sequences present on the VPI, as shown by *polymerase* chain reaction, but did not contain sequences of other chromosomal genes located outside the VPI (56). Cell-free phage preparations from a strain marked by...in certain non-O157 Shiga toxin-producing Escherichia coli clonal lineages. Infect. Immun. 67:5994-6001

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4/3,K/8 (Item 7 from file: 98)

04273994 H.W. WILSON RECORD NUMBER: BGSA00023994 (USE FORMAT 7 FOR FULLTEXT)

Interim report on genomics of Escherichia coli.

Riley, M
Serres, M. H

Annual Review of Microbiology v. 54 (2000) p. 341-411
SPECIAL FEATURES: bibl tab ISSN: 0066-4227
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 25680

TEXT:

... the same sequence is used to encode more than one polypeptide chain. The dnaX gene codes for both the t and g subunits of DNA *polymerase* III by a frameshift (218), and the speE gene codes for a polypeptide that is split to make two smaller polypeptides, which form a complex...in various approaches and methods for determining expression of genes in an entire genome under specified growth conditions (50, 413). Using a complete set of *polymerase* chain reaction primers for every gene, full-length coding regions could be laid down in an array that was available for hybridization with transcript RNAs...regulator RssB is a recognition factor that interacts with the turnover element in RpoS. Proc. Natl. Acad. Sci. USA 96:6439-44

28. Beebe JA, *Frey* PA. 1998. Galactose mutarotase: purification, characterization, and investigations of two important histidine residues, Biochemistry 37:14989-97

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...On the topology of the genetic fine structure. Proc. Natl. Acad. Sci. USA 45:1607-20

32. Berardini M, Foster PL, Loechler EL. 1999. DNA *polymerase* II (polB) is involved in a new DNA repair pathway for DNA interstrand cross-links in Escherichia coli. J. Bacteriol. 181:2878-82

33. Berg...Characterization of the membrane quinoprotein glucose dehydrogenase from Escherichia coli and characterization of a site-directed mutant in which histidine-262 has been changed to *tyrosine*. Biochem. J. 340:639-47

80a. Cromie KD, Ahmad K, Malik T, Buyukuslu N, Glass RE. 1999. Transdominant mutations in the 3'-terminal region of the rpoB gene define highly conserved, essential residues in the beta subunit of RNA *polymerase*: the GEME motif. Genes Cells 4:145-59

81. Crouvoisier M, Mengin-Lecreulx D, van Heijenoort J. 1999. UDP-N-acetyl-glucosamine:N-acetylmuramoyl-(pentapetide...12782-94

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DNA replication fidelity.

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...ABSTRACT: polymerases that provide new insights into the importance of hydrogen bonding, base pair geometry, and substrate-induced conformational changes to fidelity. These studies also reveal *polymerase* interactions with the DNA minor groove at and upstream of the active site that influence nucleotide selectivity, the efficiency of exonucleolytic proofreading, and the rate...

TEXT:

Key Words base substitutions, frameshifts, DNA *polymerase*, nucleotide selectivity, proofreading

INTRODUCTION

Efforts to understand DNA replication fidelity now span half a century. This long-standing interest reflects an appreciation among scientists in...

...the biochemistry of error discrimination during DNA synthesis.

We begin by reviewing how DNA polymerases selectively incorporate correct nucleotides. The focus is on recent DNA *polymerase* structure-function studies that address the importance of hydrogen bonding (H-bonding), base pair geometry, and conformational changes that are induced by DNA and deoxynucleoside...

...extension without proofreading. Error rates for single-base substitutions due to proofreading-deficient DNA polymerases vary from 10-3 to > 10-6, depending on the *polymerase*, the mispair, and the local sequence environment (4-6). These rates indicate that the inherent nucleotide selectivity of DNA polymerases provides a greater contribution to...

...fidelity, and led to the concept (12-14; recently reviewed in 15) that selectivity depends primarily on base pair geometry. The active site of a *polymerase* is designed to accept geometrically equivalent Watson-Crick base pairs and to reject base pairs differing from this geometry. It was further suggested (16) that...

...and Poltev (12) also hypothesized that following an initial check for steric hindrance, a second check might occur that involves a conformational transition of the *polymerase*, leading to formation of a phosphodiester bond. Evidence for induced conformational transitions comes from elegant kinetic studies of several DNA polymerases (reviewed in 3, 15...

...The actual amount of discrimination at each of these points in the reaction varies among the DNA polymerases and mispairs that have been examined.

DNA *POLYMERASE* STRUCTURE

Support for geometric selection and for the idea that correct dNTP binding

induces conformational changes needed for catalysis comes from exciting progress on the structures of DNA polymerases (33-49; reviewed in 50-52). *Polymerase* domains are composed of three subdomains--fingers, palm, and thumb--(33) that contribute to template-primer and dNTP binding. In the absence of dNTP, apoenzymes...wherein a protein structural element is somewhat distant from the primer terminus. This is exemplified in Figure 1A by the (gray) a Helix N in *polymerase* b (pol b), a helix O in bacteriophage T7 *polymerase* (T7 pol), and the b3-b4 loop in the reverse transcriptase of human immunodeficiency virus type 1 (HIV-1 RT). Binding of a correct dNTP (yellow in Figure 1A, B) induces remarkable conformational changes in the DNA and the *polymerase* that lead to assembly of the *polymerase* active site. The structures of ET-PdNTP complexes of pol b, T7 pol, and HIV-1 RT reveal that the single-stranded template nucleotide (red...

...base pair (Figure 1B, viewed from the major groove, with which there is little contact). The surface of the binding pocket is determined partly by *polymerase* interactions (purple in Figure 1B) with the minor groove edge of the templating base and with the base, sugar, and phosphates of the incoming dNTP. The surface is also defined by both nucleotides of the primer-terminal base pair (green in Figure 1B). These nucleotides interact with *polymerase* residues (not shown), in some cases via H-bonding between side chains and the N-3 atoms of purines or the O-2 atoms of...
...s) is rate limiting for misinsertion (for additional discussion, see 29-31, 43) and whether the rate-limiting step may differ depending on the DNA *polymerase*, the mispair, and the local sequence environment.

MUTATOR AND ANTIMUTATOR POLYMERASES

Recent studies (Table 1) show that polymerases containing amino acid substitutions that may alter...acceptor and donor atoms in the minor groove. More generally, this implies that differences in how polymerases interact with the DNA minor groove may underlie *polymerase*-specific variability in base substitution error rates. Another example of a mutant *polymerase* with unusual error specificity is Kf pol E710A, which preferentially misinserts pyrimidines (59). Even more unusual is HIV-1 RT R72A, which is generally an...

...higher discrimination during mismatch extension, but which is uniquely error-prone for misinsertions in a particular nucleotide sequence (60). This specificity shows that a mutant *polymerase* may yield an average replication fidelity that is higher than normal, yet paradoxically place specific sequences at very high risk of mutation.

The mutator or...

...1A) at the junction of the fingers and palm. In Taq pol open complexes (49) and a Bst pol complex with DNA (47), the homologous *tyrosine* side chain stacks against the template base, leading to the suggestion (52) that this *tyrosine* may chaperone each template base into the active site during translocation, prior to closure of the fingers.

The induced-fit hypothesis implies that the conformational changes necessary for catalysis will not be induced, or will be induced less efficiently, by the binding of an incorrect dNTP to a *polymerase*. This is supported by the observation that pol b is in an open conformation when an adeninedideoxyguanosinetriphosphate (AddGTP) mismatch is present in the active site...with a natural base pair.

One problem with the steric complementarity hypothesis is how to exclude small pyrimidinepyrimidine misinsertions that might easily fit into the *polymerase* binding pocket. Kool (73) posits that even pyrimidinepyrimidine mismatches are large enough to be sterically excluded because their Watson-Crick pairing edges are H-bonded...

...because they are not complementary and because any complementary arrangement that might occur (e.g. a wobble configuration) would produce a steric clash in the *polymerase* binding pocket. In support of this idea, the nonpolar thymidine analog dF is incorporated opposite template F with an efficiency that is 100- to 1000...
...provide a strong force to prevent misinsertions via steric exclusion.

Just how H-bonds between nucleosides and water are exchanged (or not) as a DNA *polymerase* moves from an open to a closed conformation remains an interesting issue for the future.

MISMATCH EXTENSION AND *POLYMERASE* INTERACTIONS WITH DUPLEX DNA

Since misinsertions result in base substitutions only if the terminal mismatch is extended without being proofread, the capacity of a *polymerase* to extend a mismatch is a critical determinant of replication fidelity. Mismatch extension can be considered in light of structural studies revealing that, in addition...

...site, DNA polymerases also interact extensively with the duplex template-primer (Figure 2). Chemical footprinting and fluorescence spectroscopy studies (reviewed in 50) show that the *polymerase* domain of Kf pol contacts five to eight base pairs of duplex DNA. This is consistent with the contacts seen in T7 pol, Bst pol...

...purines and the O-2 atoms of pyrimidines (green in Figure 2). Interactions in the minor groove are facilitated by a minor groove near the *polymerase* active site that is wider and shallower than that of normal B-DNA (Figure 2, 36, 38, 39, 46-49). In HIV-1 RTDNA complexes (36, 48), the duplex template-primer four to seven base pairs upstream of the *polymerase* active site is bent by about 40[degree]. T7 pol also imposes a bend to the duplex; this bend in combination with the bend in...

...pair in defining geometry in the binding pocket (green surface in Figure 1B) and at the active site. The effect of mismatches in stalling the *polymerase* extends well beyond the position of the terminal base pair. Mismatches at the third and fourth base pair positions in the duplex promote transfer of...

...to the ability to sense base pair geometry. Effects are not limited to mismatches. Elongation efficiency is reduced by DNA adducts located upstream of the *polymerase* active site (e.g. see 87-90 ...RT complexes (Figure 2). The paucity of H-bonds for HIV-1 RT in the minor groove may relate to the reported promiscuity of this *polymerase* in extending mismatched termini (81, 91). The importance of H-bonding interactions in the minor groove is also indicated by studies of the N279A/L...

...by the rate of sliding of the terminal nucleotide into the exonuclease active site on the enzyme (kSX). The rate of sliding back to the *polymerase* active site of T7 pol is reported (84) to be fast (kSP = 700/s). This provides sufficient time for removal of the terminal nucleotide but...

...other proofreading-proficient DNA polymerases (reviewed in 3, 19, 50, 95; also see 85, 96-104) also reveal the importance of the communication between the *polymerase* and exonuclease active sites. T7 pol (3, 84), T4 pol (96, 105), and to a lesser extent Kf pol (106) each proofread mismatches processively, i.e. the DNA substrate can move between the *polymerase* and exonuclease active sites without enzyme dissociation from DNA. The *polymerase* and exonuclease active sites (e.g. see Figure 4) are located [similar]30 A apart in Kf pol (33, 37), [similar]35 A apart in... 114). Frayed, single-stranded DNA preferentially binds to the exonuclease domain (37, 45, 50, 115), while correctly paired duplex template-primers preferentially bind to the *polymerase* domain (see above). Fluorescence studies with T4 pol (100) suggest that transfer of the primer terminus from the *polymerase* active site to the exonuclease active site involves formation of a preexonuclease complex containing a partially melted primer strand. In considering possible intermediates in the proofreading scheme, note that a comparison of the structures of RB69 pol and Tgo pol led to the interesting suggestion (49) that when the *polymerase* is incorporating nucleotides, the exonuclease active site may be in a closed conformation that prevents binding of single-stranded DNA, but it changes to a...
...Thus, mutations that inactivate exonuclease activity in Kf pol have little effect on polymerization, while mutations that inactivate the exonuclease activity of RB69 also affect *polymerase* activity (116).

Consistent with the critical balance between extension and excision (Figure 3), proofreading can be reduced by stimulating the rate of mismatch extension through...

...mismatch and its location, especially the sequence context in which it is embedded, as well as the nature and extent of DNA contacts with the *polymerase* and exonuclease domains.

As an alternative to processive intramolecular proofreading, a DNA *polymerase* may dissociate from the DNA following misinsertion. If the enzyme does dissociate, it may rebind to the DNA via the exonuclease active site and edit...

...extent with T7 (3) and T4 polymerases (96, 105). A mismatched substrate can also be bound and proofread by an exonuclease associated with a different *polymerase* (117) or one not associated with a *polymerase* at all (118). It remains to be seen if intermolecular proofreading occurs in vivo.

REPLICATION ERRORS INVOLVING STRAND MISALIGNMENTS

Interest in nucleotide deletion and addition...

...shown between cancer and the sequence instability of microsatellites (119, 120) and between neurodegenerative diseases and the sequence instability of triplet repeats (121). Every DNA *polymerase* whose fidelity has been examined generates deletion or addition errors during DNA synthesis in vitro (4-6, 122). Deletion and addition error rates are highly ...several different lesions (144-149) strongly support this idea.

Slippage may also be initiated during enzyme dissociation or reassociation. Indeed, lower frameshift fidelity in DNA *polymerase* correlates with lower processivity, i.e. the number of nucleotides incorporated per cycle of DNA binding-synthesis-dissociation. Thus, pol b is both less accurate...

...which contains a second DNA binding site for the 5' end of short gaps. The low frameshift fidelity may therefore reflect the capacity of the *polymerase* domain to freely dissociate and reassociate, even in a reaction that is processive by virtue of the second binding site (see Figure 3 in 152...

...with the sliding clamp, gp45.

It is also possible that misalignments are initiated during processive translocation, and modulated as the DNA processively moves between the *polymerase* and exonuclease active sites. Thus, exonuclease-deficient Kf pol, which contains two DNA binding sites separated by 30 A, is more accurate for single-base deletions in homonucleotide runs than is the 48-kDa *polymerase* domain alone, which contains only the *polymerase* active site (128). This led to the suggestion that misalignments that form during moderately processive polymerization by Kf pol may be disrupted as the DNA frays and moves to the exonuclease site, allowing for correct annealing upon movement back to the *polymerase* active site. The opposite possibility has been put forth to explain the appearance of single-nucleotide additions in homonucleotide runs generated by highly processive E...

...create an addition intermediate is much higher during reannealing of the primer terminus as the DNA moves from the exonuclease active site back to the *polymerase* active site. An alternative model for how misalignments may be initiated has been invoked to explain pol b incorporation specificity with damaged DNA (153; also...

...intermediate requires the disruption of one additional base pair relative to formation of a minus-one-base intermediate (see Figure 2 in 156).

Consistent with *polymerase* structural information, the sequence dependence of strand-misalignment infidelity also depends on the enzyme.

For example, with pol b and HIV-1 RT, the rate...modulating frameshift fidelity.

As predicted from the misalignment models discussed above, frameshift fidelity is also influenced by enzyme-substrate interactions in the vicinity of the *polymerase* active site. Y766A/S mutants of Kf pol (Table 1) are mutators for two-base deletions and for a 276-base deletion between direct repeat...

...been described (for review, see 167).

CONTRIBUTION OF ACCESSORY PROTEINS TO FIDELITY

DNA polymerases seldom if ever work alone in vivo. Biochemical studies show that *polymerase* fidelity during DNA synthesis in vitro can be modulated by accessory proteins. For example, a 46-fold increase in single-nucleotide addition fidelity is conferred to exonuclease-deficient T7 pol upon addition of thioredoxin (130), the accessory protein that confers high processivity to the *polymerase* catalytic subunit. This enhanced fidelity is consistent with the hypothesis that slippage may initiate during enzyme dissociation or reassociation (although other explanations are also possible...be enhanced by single-stranded DNA binding protein (reviewed in 6). The enhancement is small relative to the high degree of discrimination imposed by the *polymerase* and exonuclease. However, mutant alleles of yeast RPA have recently been described that promote the deletion of large numbers of nucleotides in vivo (175), consistent...

...polymerases, consistent with the idea that the DNA polymerases rather than their accessory proteins are the main determinants of replication fidelity. Proofreading by replicative DNA *polymerase* III holoenzyme contributes between 40- and 200-fold to this rate, with the base selectivity of the replication machinery contributing the balance (7). Measurements also...

...leading strand is more processive than is discontinuous synthesis of Okazaki fragments on the lagging strand, and lagging strand replication requires more than one DNA *polymerase*, one or more switches between enzymes, and the synthesis and eventual replacement of RNA primers. RNA primer replacement at the 5' ends of Okazaki fragments...

...damaged base and its replacement through synthesis catalyzed by pol b (although other repair pathways are known). Pol b is the least accurate mammalian DNA *polymerase*, with an average substitution error rate of [similar]10-3 (see 152 and references therein). If this was the error rate in vivo, base excision than that of the *polymerase* alone (but see 190). Alternatively, pol b misinsertions might be proofread by an extrinsic exonuclease (e.g. see 191, 192) or subsequently corrected by some...

...example, several decades after discovery of the three canonical E. coli DNA polymerases, we now know that this bacterium harbors at least two more. DNA *polymerase* IV (194) is the product of the DinB gene. It is an exonuclease-deficient, distributive *polymerase* required for SOS-induced untargeted frameshift mutagenesis of phage l in vivo, and prone to extension of misaligned template-primers in vitro. Another is E. coli DNA *polymerase* V (195, 196), a distributive *polymerase* comprising the UmuD'2C complex that is required for SOS mutagenesis. In combination with activated RecA protein, the b, g complex, and SSB, Pol V...

...DNA polymerases have also been described in eukaryotes. The Saccharomyces cerevisiae REV3 gene required for UV-induced mutagenesis encodes pol z (197), a nonessential DNA *polymerase* of the pol a family; pol z bypasses thymine-thymine dimers that block synthesis by many other polymerases. A putative human homolog of REV3 has...
...gene is also required for UV-induced mutagenesis in vivo, and is homologous to the E. coli DinB and UmuC proteins. REV1 encodes a DNA *polymerase* with deoxycytidyl transferase activity (199). The S. cerevisiae RAD30 gene is also homologous to E. coli DinB and UmuC and encodes DNA pol H, an enzyme that bypasses thymine-thymine dimers in vitro

(200), and whose *polymerase* activity is needed for error-free bypass of UV-induced DNA damage in vivo (201). A separate study (202) reported purification of a DNA *polymerase* from human HeLa cells that could restore the ability of extracts of xeroderma pigmentosum variant (XP-V) cells to bypass thymine-thymine dimers during SV40...

...individuality of polymerases and the fact that genomes represent literally millions of different substrates, several challenges remain for the future. The remarkable contribution of recent *polymerase* structure-function studies toward understanding replication fidelity sharpens the appetite for more information. This includes higher resolution structures of wild-type enzymes and structural information...G262A

1-3	3-27	78, 131	
W266A	1-2	1-50	78, 131

FOOTNOTES

a Values are for rates of replication error in DNA *polymerase* mutants relative to error rates observed in wild-type, exonuclease-deficient parent *polymerase*. Values in red are the ratio of the error rate of the mutant enzyme to that of the wild-type enzyme, and thus indicate a...

...DNA polymerases. (A) Subdomain movements to assemble the binding pocket for the nascent base pair. Drawings are based on the crystal structures of (left) DNA *polymerase* b in complex with gapped DNA and in complex with gapped DNA and ddCTP (Brookhaven Protein Data Bank numbers 1BPX and 1BPY, respectively); (center) unliganded...

...template nucleotide are red. The images were generated based on crystal structures of the polymerases in ternary complexes using the program GRASP (216).

Figure 2 *Polymerase* interactions with the minor groove of the duplex template-primer. The images are based on the structures of the DNA present in ternary polDNAdNTP complexes (Protein Data Bank numbers in legend to Figure 1A). Purple represents the surface of interaction between the *polymerase* and the DNA, where distances between the DNA and protein molecular surfaces are equal to or less than 1.4 A. The H-bonds to bases in the minor groove are indicated in green. For comparison with the minor groove of the DNA in the *polymerase* ternary complexes, the minor groove in unliganded B-DNA (Protein Data Bank number 1BNA) is indicated on the right. The figure was prepared using the program GRASP (216).

Figure 3 Kinetic scheme for proofreading by T7 DNA *polymerase*. The rates (all per second, taken from References 84 and 3) are shown in green for correct base pairs and in red for incorrect base pairs. The rates of sliding into the exonuclease and *polymerase* active site are designated kSX and kSP, respectively, where X and P correspond to the exonuclease and *polymerase* active sites. Double-stranded DNA is designated dsDNA, and single-stranded DNA is designated ssDNA. The kexo value is the rate of excision of single...

...are suggested to be the rate-limiting sliding of the primer terminus into the exonuclease active site kSX (3).

Figure 4 Location of exonuclease and *polymerase* active sites in Kf and RB69 polymerases. The enzymes are in ribbon representation with the *polymerase* domain in gray and the exonuclease domain in red. The catalytic residues at the *polymerase* active site (dark blue) and exonuclease active site (green) are in space-filling representation. The images were generated using Insight II version 97.0, and are based on the crystal structures of Kf pol in complex with DNA (Protein Data Bank number 1KLN) and the unliganded RB69 *polymerase* (Protein Data Bank number 1WAJ).

Figure 5 Models for errors involving misaligned template-primers. See text for description. (Adapted from Reference 122).

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TEXT:
... Since the presence of an iron-sulfur center does not affect SoxR binding to DNA, it must somehow affect the interaction of SoxR with RNA *polymerase*. One intriguing finding is that SoxR binds to the region between the s70-type -10 and -35 promoter recognition elements of the soxS promoter, which...
...71). Additional footprint analysis using Cu-5-phenyl-1, 10-phenanthroline as a probe for DNA single strands indicates that only oxidized SoxR stimulates RNA *polymerase* to form an open complex at the promoter (Figure 1) (68). These results indicate that the soxS promoter is most likely co-occupied by SoxR and RNA *polymerase* and that the oxidation/reduction state of iron sulfur centers must somehow affect the ability of SoxR to stimulate RNA *polymerase* to form an open complex. It remains to be determined how this occurs.

FNR
FNR is a global regulator responsible for controlling aerobic-anaerobic regulation...26, 50) and NADH dehydrogenase (154). Mutational analyses have defined a region in FNR that activates transcription by interacting with the a subunit of RNA *polymerase* (167a). Interestingly, many mutations that only affect repressing activity of FNR also map to the same region (61a).

Sequence analysis revealed striking similarities of FNR...

...response regulator (29, 105, 131). In vitro transcription assays demonstrated that oxygen responsive transcription of the R. meliloti nifA and fixK genes requires only RNA *polymerase*, FixL and FixJ (1, 9, 32, 116, 140). This indicates that FixL is capable of directly sensing oxygen

tension and that FixJ[similar]P is...

...binding effector domains (29, 52, 90). The mechanism of FixJ[similar]P-mediated transcription activation is not known beyond the fact that it activates RNA *polymerase* holoenzyme that contains s70 (140).

Extensive in vitro analyses have determined that the autophosphorylation of FixL, rather than phosphotransfer to FixJ, is the step that...this event is linked to the propagation of long-range changes in FixL conformation (Figure 1), mediated in part by deprotonation of one or more *tyrosine* residues that inactivates kinase activity (107).

Besides oxygen, the in vitro kinase activity of FixL is also influenced by other factors such as Mn ion...of NifA to its target sequence (7) but does affect NifA triphosphatase activity, which is needed for the formation of open complex by s54-RNA *polymerase* (44). On the other hand, NifL from K. pneumoniae does affect NifA binding to the target sequence (118) but not its triphosphatase activity (13). In this case it has been suggested that NifL affects NifA binding as well as interactions with s54-RNA *polymerase*.

In addition to redox, NifL modulates NifA activity in response to energy and the fixed nitrogen status of the cell. Specifically, NifL of A. vinelandii...
...solution as a tetramer (98) and belongs to the class I activators that interact with the carboxyl-terminal region of the a-subunit of RNA *polymerase* to promote transcription activation. OxyR acts cooperatively to increase binding of s70--containing RNA *polymerase* to the katG and oxyS promoters, presumably through direct contact with the a-subunit (99, 158).

OxyR synthesis occurs even in the absence of H2O2...genes in many diazotrophs. NifA is a member of the s54 bacterial enhancer-binding family, and it exhibits an ATPase activity needed for s54-RNA *polymerase* to form an open complex (reviewed in 46, 119). NifA protein from most species typically contains three domains. The amino-terminal domain is dispensable for...

...be required to prevent NifA from being inactivated by NifL under derepressing conditions (38). The central domain, which is suggested to interact with s54-RNA *polymerase*, possesses the conserved putative nucleotide-binding site. The carboxyl-terminal domain of NifA contains a HTH-type DNA-binding motif.

As already mentioned in this...

...by Morett et al (117) demonstrated that oxygen affects not only the DNA-binding activity of NifA, but also its ability to stimulate s54-RNA *polymerase* to form an open complex.

Alignments between NifA homologs indicated a striking difference between oxygen-tolerant NifA proteins from K. pneumoniae and A. vinelandii, and...

...ability to form a dimer that binds DNA. SoxR has stable iron sulfur centers that, upon changes in redox state, affect its interaction with RNA *polymerase*. FixL utilizes heme as a cofactor to facilitate a conformational change in response to the presence of oxygen. NifL uses a FAD as a cofactor...Hennecke H. 1987. Direct response of Bradyrhizobium japonicum nifA-mediated nif gene regulation to cellular oxygen status. Mol. Gen. Genet. 209:621-26

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4/3,K/11 (Item 10 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

04014395 H.W. WILSON RECORD NUMBER: BGSI99014395 (USE FORMAT 7 FOR FULLTEXT)
Excitation-contraction coupling in gastrointestinal and other smooth muscles.
AUGMENTED TITLE: review
Bolton, T. B
Prestwich, S. A; Zholos, A. V
Annual Review of Physiology (Annu Rev Physiol) v. 61 ('99) p. 85-115
SPECIAL FEATURES: bibl ISSN: 0066-4278
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 16182

(USE FORMAT 7 FOR FULLTEXT)

...ABSTRACT: for inhibitory signal molecules increases the activity of protein kinases through increases in cAMP or cGMP and often hyperpolarizes the cell. Other receptors link to *tyrosine* kinases, which trigger signal cascades interacting with trimeric G-protein systems. With permission, from the Annual Review of Physiology, Volume 61, 1999, by Annual Reviews...

TEXT:
... channels. Some, such as the P2X-receptor (a purinoceptor), combine a ligand-binding site and an ion channel (159). Many receptors for growth factors have *tyrosine* kinase activity, and some have been implicated in regulation of Ca2+ i (76, 178). Receptors can be divided conveniently into those binding signal molecules that...

...IP3 production (62, 97), as first shown by Best & Bolton (16).

The isoform PLC-g is linked to receptors for growth factors which have intrinsic *tyrosine* kinase activity; activation of some G-protein-coupled receptors has been reported to cause phosphorylation of PLC-g in vascular SM (174). A rise in...

...other pathways. Arachidonic acid, besides being a precursor for prostaglandins and related eicosanoids, has actions of its own on channel function (149, 162, 186), on *tyrosine* kinase activity (see e.g. 26), and on myosin phosphorylation (195). Phosphatidic and arachidonic acids can activate PLC-g (174). In recent years a large...coupled and may modulate ion channel activity directly (and thus electrical activity) or via phosphorylation. In addition, a number of receptors are known to activate *tyrosine* kinases directly without the intervention of G proteins and to interact with G protein-coupled systems. Although a change in Ca2+ i is the most...C1723-28
25. Bootman M. 1994. Questions about quantal Ca2+ release. Curr. Biol. 4:169-72
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27. Buryi VA, Gordienko DV, Shuba MF. 1994. Two kinds of spatially separated caffeine-sensitive...K+ channel from canine colonic smooth muscle. Proc. Natl. Acad. Sci. USA 90:9659-63
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77. Hatakeyama N, Wang Q, Goyal RK, Akbarali...71:732-41
119. Ledbetter MW, Preiner JK, Louis CF, Mickelson JR. 1994. Tissue distribution of ryanodine receptor isoforms and alleles determined by reverse transcription *polymerase* chain reaction. J. Biol. Chem. 269:31544-51
120. Lee HK, Bayguinov O, Sanders KM. 1993. Role of nonselective cation current in muscarinic responses of...

...Hepler PK, Gross DJ. 1993. Independent modes of propagation of calcium waves in smooth muscle cells. J. Cell Sci. 104:1101-7
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178. Salvo JD, Nelson SR, Kaplan N. 1997. Protein *tyrosine* phosphorylation in smooth muscle: a potential coupling mechanism between receptor activation and intracellular calcium. Proc. Soc. Exp. Biol. Med. 214:285-301
179. Sanders KM...

4/3,K/12 (Item 11 from file: 98)

03805285 H.W. WILSON RECORD NUMBER: BGSI98055285 (USE FORMAT 7 FOR FULLTEXT)
Regulation of acetate metabolism by protein phosphorylation in enteric bacteria.
Cozzone, Alain J
Annual Review of Microbiology (Annu Rev Microbiol) v. 52 ('98) p. 127-64
SPECIAL FEATURES: bibl il ISSN: 0066-4227
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 17608

(USE FORMAT 7 FOR FULLTEXT)

TEXT:
... of the serine with other amino acids (lysine, cysteine, alanine, asparagine, or glutamine) produces active enzymes that bind both isocitrate and NADPH. Neither threonine nor *tyrosine*, when substituted for serine at the phosphorylation site, is detectably phosphorylated (39, 178).

The structure of the phosphorylated form of IDH from E. coli has... promoter region of the aceBAK operon shows that the repressor binds to a 35-nucleotide sequence that largely overlaps the -35 binding site of RNA *polymerase* (28). Such topological coincidence between the operator and promoter regions indicates that the IclR repressor and the transcription enzyme will compete for the same binding...action would then resemble that of CRP activation, in which the binding of the protein bends the DNA and facilitates its direct contact with RNA *polymerase* (98, 151).
The N-terminal domain of E. coli FruR, containing the first 60 amino acids, has been overproduced and purified to homogeneity after cloning...of 170[degree] of the DNA helix (JF Prost, AJ Cozzone, unpublished data).

Stimulation of aceBAK expression is also induced by the interaction of RNA *polymerase* with a particular DNA region termed the upstream (UP) module. It has been shown that, in addition to its two major determinants (the -10 and -35 hexamers), the promoter strength of the E. coli RNA *polymerase* can be greatly increased by a third cis-acting recognition element, the UP module, which spans an (A+T)-rich region interacting with the a...

...region of aceBAK contains an UP element centered around base -50 (Figure 3), which can form a stable and specific complex with either the RNA

polymerase holoenzyme or with its a subunit alone (130). The removal of certain bases between positions -32 to -50 of the ace promoter interferes with the...

...a subunit, while the elimination of single bases from either strand of the UP element results, in contrast, in an enhanced binding affinity of RNA *polymerase*. It therefore appears that disruption of the DNA helix in this particular region promotes a local DNA flexibility that stabilizes the RNA *polymerase*-promoter complex and, consequently, increases the aceBAK expression (130). More generally, it is interesting to note that the different factors (UP, IHF, FruR) that stimulate...Mol. Biol. 220:13-16

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4/3,K/13 (Item 12 from file: 98)

03796043 H.W. WILSON RECORD NUMBER: BGSI98046043 (USE FORMAT 7 FOR FULLTEXT)
Modified oligonucleotides: synthesis and strategy for users.
AUGMENTED TITLE: review
Verma, Sandeep
Eckstein, Fritz
Annual Review of Biochemistry (Annu Rev Biochem) v. 67 ('98) p. 99-134
SPECIAL FEATURES: bibl il ISSN: 0066-4154
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 14342

(USE FORMAT 7 FOR FULLTEXT)

TEXT:
... bases, sugars, or phosphate groups is a viable alternative to chemical synthesis. Enzymatic incorporation of modified nucleoside triphosphates, with T7 or a similar phage RNA *polymerase*, is particularly well suited for template-directed transcription reactions, provided that they are good substrates for the *polymerase*. This requirement limits the number of modified nucleotides that can be used in transcription reactions; thus only a few modifications can be enzymatically introduced into oligoribonucleotides. For oligodeoxynucleotides, these modifications must be made by chain extension of a primer annealed to a template, through use of a DNA *polymerase* such as the Klenow fragment of Escherichia coli DNA *polymerase* I.

Among internucleotidic linkages, phosphorothioate is the most common enzymatically introduced modification, as all of the four nucleoside a-thiotriphosphates are good substrates for DNA sulfur introduces chirality at the phosphorus center. Only the Sp-diastereomer of nucleoside a-thiotriphosphates is a good substrate for the *polymerase*. The enzymatic incorporation proceeds with inversion of configuration at phosphorus,

resulting in the formation of the Rp internucleotidic linkage. Therefore, enzymatic synthesis is limited to...

...22). This methodology has been applied to the synthesis of all Rp-phosphorothioate transcripts (23) and oligodeoxynucleotides through use of either a modified T7 DNA *polymerase* (24) or Taq DNA *polymerase* (25). The applications of phosphorothioate modification are discussed later in this chapter.

2'-Deoxynucleoside triphosphates were the first sugar-modified analogs to be examined as substrates for T7 RNA *polymerase* (26). However, in their presence, transcription was aborted 30[percent] of the time. Recently, the use of Mn2+ instead of Mg2+, in carefully controlled ratios ...

...O-methyl nucleotides, which are not incorporated under normal transcription conditions. Efficient incorporation of deoxynucleoside triphosphates can also be achieved by a mutant T7 RNA *polymerase*, without the requirement for special transcription conditions (28). 2'-Amino-2'-deoxynucleoside triphosphates are good substrates for the wild-type enzyme. As an example, synthesis...

...nt in length has been achieved (Figure 1; 29). However, corresponding 2'-fluoro-2'-deoxy analogs are less readily incorporated (29). The mutant T7 RNA *polymerase* improves the incorporation of the 2'-fluoro derivatives (30).

T7 RNA *polymerase* normally initiates transcription with a guanosine triphosphate, but it can also accept other guanosine derivatives such as guanosine 5'-monophosphorothioate (31), guanosine 5'-b-thiotriphosphate... chemical viewpoint, reactivity of the phosphorothioate group should be only marginally lower than that of the phosphate diester. One study involving mechanistic investigation of the *polymerase* activity of Klenow DNA *polymerase* (71) and another study investigating the interaction of GTPgS with transducin-a (72) have pinpointed the source of the rate difference. It was suggested that...primers by the 3'-exonuclease activity of the thermostable DNA polymerases Vent and Pfu (102), an important consideration for the use of such primers in *polymerase* chain reactions.

Nuclease resistance of phosphorothioate internucleotide linkages, particularly to the restriction enzyme NciI, is the basis of an oligonucleotide-directed, site-specific mutagenesis procedure... oligonucleotide primers containing multiple substitutions of 5-nitroindole (187, 188) and 3-nitropyrrole (189, 190) has been studied and compared in DNA sequencing and in *polymerase* chain reactions. These ...resistance to nucleases (200). Moreover, these modifications can be introduced easily during aptamer selection because the corresponding nucleotide triphosphates are good substrates for T7 RNA *polymerase* (29, 30). When these analogs were used, nuclease-resistant aptamers were isolated against the basic fibroblast growth factor (212), human thyroid-stimulating hormone (213), a ...forming C4' adducts were incorporated in DNA templates to investigate structural the requirement of the Klenow fragment of E. coli DNA pol I (223). The *polymerase* halts transiently at inversions while adduct-forming modifications completely inhibit the DNA synthesis.

The furanose ring oxygen has also been replaced with a pyrrolidine ring...
...of change in fluorescence intensity of 2AP (228). Several reports have described the use of 2AP-containing oligonucleotides to study base-pairing interactions in DNA *polymerase* 3'-5'-exonuclease proofreading (229-231), kinetics of nucleotide incorporation with the Klenow fragment and T4 DNA *polymerase*, (232, 233), and the helicase-catalyzed unwinding of duplex DNA (234). In one study, Mg2+ ion-induced conformational perturbations in the hammerhead ribozyme tertiary structure...

...template/primer oligonucleotides, where a fluorescent dansyl probe was appended at various nucleotide positions from the 3'-end of the primer, indicated that the Klenow *polymerase* remains in contact with the template/primer up to six nucleotides from the 3'-end (238). Similarly, contacts between a 42-mer oligonucleotide and the...

...for polymerization into a template/primer for the determination of dissociation constants of DNA and the dNTPs for the Klenow fragment of E. coli DNA *polymerase* I (240).

NONBASE ATTACHMENT Fluorescent dyes have been attached to oligodeoxynucleotides by the reaction of internucleotidic phosphorothioates with 5-iodoacetamido-eosin and -fluorescein (241). Distances...telomeric DNA containing 5-bromodeoxyuridine has been cross-linked to the Oxytricha telomeric protein (277). Two of the three cross-links were traced to the *tyrosine* residues in the hydrophobic region, suggesting that intercalation plays a major role in protein-telomeric DNA binding.

The 5-position of uridine and deoxyuridine can...

...an amino linker, and the nucleotide has been incorporated chemically into oligonucleotides to allow study of the contact with the Klenow fragment (279), T4 DNA *polymerase* (280), and E. coli DNA *polymerase* III (281).

In one study, multiple 5-methyleneaminouridine triphosphate residues were introduced in oligoribonucleotides by T7 RNA *polymerase* transcription of synthetic DNA templates (282). The free amino group in modified uridine was postsynthetically derivatized, at the RNA level, with an azirinyl group-containing...Reha-Krantz LJ. 1996. J. Biol. Chem. 271:28903-11

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233. *Frey* MW, Sowers LC, Millar DP, Benkovic SJ. 1995. Biochemistry 34:9185-92

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4/3,K/14 (Item 13 from file: 98)

03796042 H.W. WILSON RECORD NUMBER: BGSI98046042 (USE FORMAT 7 FOR FULLTEXT)

Ribonucleotide reductases.

AUGMENTED TITLE: review

Jordan, A
Reichard, P

Annual Review of Biochemistry (Annu Rev Biochem) v. 67 ('98) p. 71-98
SPECIAL FEATURES: bibl il ISSN: 0066-4154
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 11795

(USE FORMAT 7 FOR FULLTEXT)

TEXT:

... oxygen-linked diferric center, whereas class III b2 contains an iron-sulfur cluster. The amino acid radical in class I enzymes is located on a *tyrosine* residue of b itself, whereas the glycyl radical of class III is located on a. Class II enzymes lack the small subunit and contain no ...during G1, mRNA synthesis is initiated but blocked in the first intron by a unique cell cycle-dependent transcriptional block (122). During S-phase the *polymerase* is able to read through the block and transcribe the whole gene. R2-mRNA stability is regulated similarly to R1-mRNA by specific RNA-protein...Biol. Chem. 264:9164-70

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...32:14102-10

88. Broderick JB, Duderstadt RE, Fernandez DC, Wojtuszewski K, Henshaw TF, Johnson MK. 1997. J. Am. Chem. Soc. 119:7396-97

89. *Frey* PA, Reed GH. 1993. Adv. Enzymol. Relat. Areas Mol. Biol. 66:1-39
90. Reed GH, Bollinger MD. 1995. Methods Enzymol. 258:362-77
91...

4/3,K/15 (Item 14 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

03751721 H.W. WILSON RECORD NUMBER: BGSI98001721 (USE FORMAT 7 FOR FULLTEXT)
Gene targeting and the biology of learning and memory.
Silva, Alcino J
Smith, Alan M; Giese, Karl Peter
Annual Review of Genetics (Annu Rev Genet) v. 31 ('97) p. 527-46
SPECIAL FEATURES: bibl ISSN: 0066-4197
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 9334

(USE FORMAT 7 FOR FULLTEXT)

TEXT:
... M.
A number of mutations affect both LTP and L&M. For example, genetic deletions of the a-Ca2+-calmodulin kinase II (aCaMKII) (73), Fyn *tyrosine* kinase (31), type I adenylate cyclase (86), NMDA receptor e1 subunit (69), and metabotropic glutamate receptor 5 (mGluR5) (50) all affect E-LTP to some...to network processing and plasticity. In Long Term Potentiation: A Debate of Current Issues, ed. MBaJ Davis, pp. 425-35. Cambridge, MA: MIT Press
27. *Frey* U, Krug M, Reymann KG, Matthies H. 1988. Anisomycin, an inhibitor of protein synthesis, blocks late phases of LTP phenomena in the hippocampal CA1 region...

...the basal ganglia. Curr. Opin. Neurobiol. 5:733-41.
33. Gu H, Marth JD, Orban PC, Mossmann H, Rajewsky K. 1994. Deletion of a DNA *polymerase* beta gene segment in T cells using cell type-specific gene targeting. Science 265:103-6
34. Gu H, Zou Y-R, Rajewsky K. 1993...

4/3,K/16 (Item 15 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

03751719 H.W. WILSON RECORD NUMBER: BGSI98001719 (USE FORMAT 7 FOR FULLTEXT)
The Tao of stem cells in the germline.
AUGMENTED TITLE: Drosophila, mammals and C. elegans
Lin, Haifan
Annual Review of Genetics (Annu Rev Genet) v. 31 ('97) p. 455-91
SPECIAL FEATURES: bibl il ISSN: 0066-4197
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 17633

(USE FORMAT 7 FOR FULLTEXT)

TEXT:
... from 530 mm3 to 2380 mm3 of postnatal gonocytes (11). There also appears to be a decrease in the level of the c-kit receptor *tyrosine* kinase RNA that roughly correlates with the entry of PGC into nonmitotic gonocytes (122, 148), even though the signal is present during the transition and...mosaics of Drosophila. Wilhelm Roux Arch. 184:41-56
172. Seydoux G, Dunn MA. 1997. Transcriptionally-repressed germ

cells lack a subpopulation of phosphorylated RNA *polymerase* II in early embryos of C. elegans and D. melanogaster. Development 124:2191-201
...differentiation of the gonads in the Drosophila embryo. Proc. Natl. Acad. Sci. USA 27:484-89
176. Sorrentino V, Giorgi M, Geremia R, Besmer P, *Rossi* P. 1991. Expression of the c-kit proto-oncogene in the murine male germ cells. Oncogene 6:149-51
177. Spradling A. 1993. Developmental genetics...

4/3,K/17 (Item 1 from file: 370)
DIALOG(R)File 370:Science

00508603 (USE 9 FOR FULLTEXT)
NEUROSCIENCE: Enhanced: RNA, Whither Goest Thou?
Tiedge,Henri; Bloom, Floyd E.; Richter, Dietmar
Science Vol. 283 No. 5399 pp. 186
Publication Date: 01/08/1999 (990108) Publication Year: 1999
Document Type: Journal ISSN: 0036-8075
Language: English
Section Heading: Perspectives
Word Count: 3652

(THIS IS THE FULLTEXT)

...Text: to the 3 (cent) untranslated region (3 (cent) UTR) (5, 6) but also to parts of the coding region (6). In the noncoding short RNA *polymerase* III transcript BC1 RNA (152 nucleotides) [HN8], a dendritic targeting element is contained within a 5 (cent) region of no more than 62 nucleotides (3...although it remains to be seen whether axonal expression of these receptors plays any functional role , for example, in axonal guidance mechanisms. The mRNA for *tyrosine* hydroxylase, the rate-limiting enzyme for catecholamine synthesis [HN15], can be detected in the cerebellum and the striatum. Because these regions contain no catecholaminergic cell...

...in proof. Activity-dependent polyadenylation of dendritic CaMKIIa mRNA may constitute an additional mechanism for regulating translation at the synapse (28).
References and Notes

* U. *Frey* and R. G. Morris, Nature 385 , 533 (1997) [Medline].
* O. Steward, Neuron 18, 9 (1997) [Medline].
* I. A. Muslimov et al., J. Neurosci. 17, 4722...Australia. The Howard Hughes Medical Institute provides a research summary titled "Information coding in the olfactory system" by L. Buck, Department of Neurobiology, Harvard University.

* *Tyrosine* hydroxylase and catecholamine are defined in the On-Line Medical Dictionary. A discussion of catecholamines is provided on the THCME Medical Biochemistry Page.

* The magnocellular...

4/3,K/18 (Item 1 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

02190911 SUPPLIER NUMBER: 101531541 (USE FORMAT 7 OR 9 FOR FULL TEXT)
New insights on oxidative stress and diabetic complications may lead to a "causal" antioxidant therapy. (Reviews/Commentaries/Position Statements).
Ceriello, Antonio
Diabetes Care, 26, 5, 1589(8)

May,
2003
PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0149-5992
LANGUAGE: English RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 6532 LINE COUNT: 00565

TEXT:

...in turn damages DNA. DNA damage is an obligatory stimulus for the activation of the nuclear enzyme poly(ADP-ribose) po lymerase. Poly(ADP-ribose) *polymerase* activation in turn depletes the intracellular concentration of its substrate (NAD.sup.+), slowing the rate of glycolysis, electron transport, and ATP formation, and produces an...

...would also be associated with other promising tools such as LY 333531, PJ34, and FP15, which block the protein kinase (beta) isoform, poly(ADP-ribose) *polymerase*, and peroxynitrite, respectively. While waiting for these focused tools, we may have other options: thiazolinediones, statins, ACE inhibitors, and angiotensin 1 inhibitors can reduce intracellular...

... the peroxynitrite anion (34). The peroxynitrite anion is cytotoxic because it oxidizes sulfydryl groups in proteins, initiates lipid peroxidation, and nitrates amino acids such as *tyrosine*, which affects many signal transduction pathways (34). The production of peroxynitrite can be indirectly inferred by the presence of nitrotyrosine (39).

The possibility that diabetes...

...hyperglycemia (44) is selectively associated with levels of nitrotyrosine found in those cells

PEROXYNITRITE, DNA DAMAGE, AND ENDOTHELIAL DYSFUNCTION: THE ROLE OF POLY(ADP-RIBOSE) *POLYMERASE* ACTIVATION -- Peroxymtnte is a potent initiator of DNA single-strand breakage, which is an obligatory stimulus for the activation of the nuclear enzyme poly(ADP-ribose) *polymerase* (48). As described above, when endothelial cells respond to high glucose, reactive nitrogen and oxygen species generation occurs (49). These reactive species trigger DNA single-strand breakage, which induces a rapid activation of poly(ADP-ribose) *polymerase* (49). The role of hyperglycemia and related oxidative stress in producing DNA damage is supported by the recent findings that increased amounts of 8-hydroxyguanine...

...correlated and can be reduced by the control of hyperglycemia and by the use of the antioxidants probucol and vitamin E (50).

Poly(ADP-ribose) *polymerase* activation in turn depletes the intracellular concentration of its substrate (NAD.sup.+), slowing the rate of glycolysis, electron transport, and ATP formation, and produces the...

...process results in acute endothelial dysfunction in diabetic blood vessels (48). The possibility of normalizing diabetic endothelial dysfunction using a specific of poly(ADP-ribose) *polymerase* inhibitor, PJ34, supports this evidence (52,53).

A NEW THERAPEUTIC APPROACH: THE "CAUSAL" ANTIOXIDANT THERAPY -- As previously stated, convincing evidence is now available about the...

...patients has been reported (63,64).

Other promising tools are LY 333531, PJ34, and FP15, which block the protein kinase (beta) isoform, poly(ADP-ribose) *polymerase*, and peroxynitrite, respectively. Not surprisingly, they have been shown to ameliorate the endothelial dysfunction induced by hyperglycemia (52,53,65, 66). LY 333531 has been of peroxynitrite (48); however, poly(ADP-ribose) (*polymerase*.sup.-/-) mice show that after coronary occlusion and reperfusion, nitrotyrosine staining is markedly reduced by PJ34 (68). There is evidence that poly(ADP-ribose) *polymerase* inhibition can suppress the expression of iNOS (69,70) and that poly (ADP-ribose) *polymerase* can regulate the function of mitochondria in oxidatively challenged cells: poly (AIDP-ribose) *polymerase* inhibitors or poly(ADP-rib ose) *polymerase* deficiency can suppress mitochondrial permeability transition and mitochondrial oxidant generation (71). Because mitochondria represent a principal source of reactive oxidants in endothelial cells placed in high

glucose (22) maybe that poly(ADP-ribose) *polymerase* inhibition suppresses nitrotyrosine generation preserving mitochondrial integrity.

FP15 is a potent peroxynitrite decomposition catalyst (66). It inhibits *tyrosine* nitration and reduces the toxicity of peroxynitrite for (beta)-cells and vascular endothelium during the development of diabetes in rats (66). Therefore, in the near future, a causal antioxidant therapy may include SOD and catalase mimetics, L-propionyl-camitine, lipoic acid, protein kinase C(beta) and poly (ADP-ribose) *polymerase* inhibitors, and peroxynitrite catalysts. This combination would aim to block the noxious cascade activated by hyperglycemia through the overproduction of superoxide and NO.

However, while...of the zinc-thiolate complex and uncoupling of endothelial nitric oxide synthase by peroxynitrite. J Clin Invest 109:817-826, 2002

(39.) Ischiropoulos H: Biological *tyrosine* nitration: a pathophysiological function of nitric oxide and reactive oxygen species. Arch Biochem Biophys 356:1-11, 1998

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...postprandial generation. Diabetes Care 25:1439-1443, 2002

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...F, Pacher P, Mabley JG, Liaudet L, Szabo B, Szabo C: Rapid reversal of the diabetic endothelial dysfunction by pharmacological inhibition of poly(ADP-ribose) *polymerase* activation. Circ Res 89:684-691, 2001

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...de la Rubia G, Stoclet JC, de Murcia G: Resistance to endotoxic shock as a consequence of defective NF-kappaB activation in poly (ADP-ribose) *polymerase*-1 deficient mice. EMBO J 18:4446-4454, 1999

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4/3,K/19 (Item 2 from file: 149)

02040880 SUPPLIER NUMBER: 80392953 (USE FORMAT 7 OR 9 FOR FULL TEXT)

Characterization of the annexin I gene and evaluation of its role in type 2 diabetes. (Brief Genetics Report).

Lindgren, Cecilia M.; Nilsson, Anita; Orho-Melander, Marju; Almgren, Peter; Groop, Leif C.

Diabetes, 50, 10, 2402(4)
Oct,
2001
PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0012-1797
LANGUAGE: English RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 3408 LINE COUNT: 00308

... of the exon/intron boundaries of the ANXA1 gene and to confirm the published cDNA sequence. Human genomic DNA extracted from lymphocytes was

amplified using *polymerase* chain reaction (PCR) as previously described (21) (GeneAmp PCR system 9600; Perkin Elmer, Foster City, CA). The exon/intron boundary between intron 1 and exon...dependent (type 2) diabetes genes reveals a major susceptibility locus on chromosome 2. Nat Genet 13(2):161-166, 1996

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...1988

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(23.) Orita M, Suzuki Y, Sekiya T, Hayashi K: Rapid and sensitive detection of point mutations and DNA polymorphisms using the *polymerase* chain reaction. Genomics 5:874-879, 1989

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...in revised form 8 July 2001.

ANXA1, annexin 1; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IVS, intronic variance sequence; NPL, nonparametric linkage; PCR, *polymerase* chain reaction; SBE, single base extension; SSCP, single-strand conformation polymorphism; TDT, transmission disequilibrium test; UTR, untranslated region.

4/3,K/20 (Item 3 from file: 149)

01897073 SUPPLIER NUMBER: 61397299 (USE FORMAT 7 OR 9 FOR FULL TEXT)

T Cell-Based Immunotherapy For Cancer: A Virtual Reality?

Lum, Lawrence G.
Ca, 49, 2, 1
March,
1999
PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0007-9235
LANGUAGE: English RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 15657 LINE COUNT: 01293

... in HNSCC (head and neck squamous cell carcinoma) patients. Head & Neck 1998;20:476.

(112.) Cayota A, Vuillier F, Siciliano J, Dighiero G: Defective protein *tyrosine* phosphorylation and altered levels of p59fyn and p561ck in CD4 T cells from HIV-1 infected patients. Int Immunol 1994;6:611-621.

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(227.) Jeffreys AJ, Wilson V, Neumann R, et al: Amplification of human minisatellites by the *polymerase* chain reaction: Towards DNA fingerprinting of single cells. Nucleic Acids Res 1988; 16:10953-10971.

(228.) Wolff RK, Nakamura Y, White R: Molecular characterization of S, Barnett L, Bourhis JH, et al: Myeloid and lymphoid chimerism after T-cell-depleted bone marrow transplantation: Evaluation of conditioning regimens using the *polymerase* chain reaction to amplify human minisatellite regions of genomic DNA. Blood 1992;80:3235-3241.

(232.) Bader P, Beck J, *Frey* A, et al: Serial and quantitative analysis of mixed hematopoietic chimerism by PCR in patients with acute leukemias allows the prediction of relapse after allogeneic...

...marrow transplantation. Oncol Rep 1998;5:281-285.
(234.) Drobyski WR, Endean DJ, Klein JP, Hessner MJ: Detection of BCR/ABL RNA transcripts using the *polymerase* chain reaction is highly predictive for relapse in patients transplanted with unrelated marrow grafts for chronic myelogenous leukaemia. Br J Haematol 1997;98:458-466...

4/3,K/21 (Item 4 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01841998 SUPPLIER NUMBER: 54772185 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Effects of Overexpression of Human GLUT4 Gene on Maternal Diabetes and Fetal Growth in Spontaneous Gestational Diabetic C57BLKS/J (Lepr.sup.db/+) Mice.(Abstract)
Ishizuka, Tatsuya; Klepcyk, Patrick; Liu, Sha; Panko, Laura; Liu, Shifan; Gibbs, E. Michael; Friedman, Jacob E.
Diabetes, 48, 5, 1061
May,
1999
DOCUMENT TYPE: Abstract PUBLICATION FORMAT: Magazine/Journal; Refereed
ISSN: 0012-1797 LANGUAGE: English RECORD TYPE: Fulltext
TARGET AUDIENCE: Professional
WORD COUNT: 7817 LINE COUNT: 00686

TEXT:
...During pregnancy, fasting plasma glucose and hepatic glucose production were twofold greater in db/+ than +/+ mice, despite similar insulin levels. In skeletal muscle, insulin-stimulated *tyrosine* phosphorylation was decreased in pregnant +/+ mice, and even more so in db/+ mice: insulin receptor (Beta) (IR-(Beta)), +/+ 34%, db/+ 57% decrease, P (is less...
... receptors to the movement of glucose transporters to the muscle cell surface are partially understood. Insulin stimulates the receptor to undergo autophosphorylation, thereby enhancing the *tyrosine* kinase activity of the (Beta) subunit of the receptor toward other protein substrates (16-18). Phosphorylation of insulin receptor substrate 1 (IRS-1) (and IRS-2) on multiple *tyrosine* residues after insulin treatment has been shown to be important in coupling the insulin receptor to glucose uptake. For example, in mice with a gene...the nearest 0.01 g. Subcutaneous fat mass was not measured in these studies. The presence of the hGLUT4 transgene was assessed in pups by *polymerase* chain reaction (PCR) of total genomic DNA, as described (32). The mutant db gene was determined in DNA from fetuses using a PCR-based assay...

...sub.2) and (CO.sub.2) in room air and within the chamber, multiplied by the flow rate, and corrected to standard temperature and pressure.
Tyrosine phosphorylation and Western blotting of insulin receptor, IRS-1, and p85(Alpha). Insulin-stimulated *tyrosine* phosphorylation of insulin receptor (IR), IRS-1, and the p85(Alpha) regulatory subunit of PI 3 kinase was analyzed in skeletal muscle of intact mice...An example autoradiogram is shown in Fig. 2A, and the results of multiple experiments were quantified by scanning densitometry. Insulin increased insulin receptor (Beta)-subunit *tyrosine* phosphorylation up to 10-fold in muscles of nonpregnant +/+ mice. During pregnancy, however, insulin-stimulated receptor autophosphorylation decreased by 34 (+ or -) 7 and 57 (+ or...

...P (is less than) 0.01) in pregnant +/+ and db/+ mice, respectively, compared with nonpregnant +/+ mice. The patterns for IRS-1 and p85(Alpha) subunit *tyrosine* phosphorylation were similar, with 35-45 and 61-65% reductions in +/+ and db/+ mice, respectively (P (is less than) 0.01). Furthermore, the levels of...

...ILLUSTRATION OMITTED)
Effect of overexpression of human GLUT4 gene on db/+ pregnant mice and fetal weight. Figure 3A shows a representative example comparing insulin-induced *tyrosine* phosphorylation in skeletal muscle from pregnant

db/+ and db/+TG6 mice. In db/+TG6 mice, insulin increased the level of *tyrosine* phosphorylation of IR(Beta), IRS-1, and p85(Alpha) by 210 (+ or -) 23, 185 (+ or -) 16, and 202 (+ or -) 21%, respectively (P (is less than) 0.01), over the levels in pregnant db/+ mice. Despite these increases in *tyrosine* phosphorylation, there were no changes observed in the levels of IR(Beta), IRS-1, or p85(Alpha) signaling proteins in muscles of the db/+TG6...of pregnancy. An increase in maternal plasma corticosterone has been observed during early gestation, and there is evidence that treatment with excess glucocorticoids can reduce *tyrosine* phosphorylation of IR(Beta) and IRS-1 as well as PI-3 kinase activity in skeletal muscle and liver (38). Interestingly, we also observed a...

...These findings suggest that changes in the early steps of insulin-signaling cascade may play a role in insulin resistance in pregnancy, and that reduced *tyrosine* phosphorylation of the insulin receptor and related proteins may provoke further muscle insulin resistance in GDM. Although the transgenic mice and single gene mutations used...

...overexpression can increase IR(Beta), IRS-1, and p85(Alpha) phosphorylation by twofold in skeletal muscle, despite no change in expression of these proteins. How *tyrosine* phosphorylation is modified by increased GLUT4 is unknown, but it is possible that improvement is acquired as a result of the correction in glucose homeostasis...

...was significantly reduced in db/+TG6 mice, suggesting perhaps that circulating TNF-(Alpha) or possibly free fatty acids could be involved in the inhibition of *tyrosine* phosphorylation in pregnant db/+ mice and restoration in the db/+TG6 mice, in addition to increased GLUT4 levels.

One of the interesting findings of these...SB, Sims EA: Longitudinal changes in insulin resistance and insulin release in non-obese pregnant women. Am J Obstet Gynecol 165:1667-1671, 1991

(9.) *Rossi* G, Sherwin RS, Penzias AS, Lapaczewski P, Jacob RJ, Shulman GI, Diamond MP: Temporal changes in insulin resistance and secretion in 24 h fasted conscious...

...of the (Beta)-subunit of its own receptor. Science 217:185-187, 1982

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(18.) Wilden PA, Siddle K, Haring...genes. Diabetes Rev 5:177-269, 1997

(38.) Giorgino F, Almahfouz A, Goodyear LJ, Smith, RJ: Glucocorticoid regulation of insulin receptor and substrate IRS-1 *tyrosine* phosphorylation in rat skeletal muscle in vivo. J Clin Invest 91:2020-2030, 1993

(39.) Saad MJA, Maeda L, Brenelli SL, Carvalho CRO, Paiva RS...

...22 January 1999.

E.M.G. holds stock in Pfizer.

ECL, enhanced chemiluminescence; GDM, gestational diabetes mellitus; IR, insulin receptor; IRS, insulin receptor substrate; PCR, *polymerase* chain reaction; PI, phosphatidylinositol; SGA, small for gestational age; STZ, streptozotocin; TG, transgenic; TNF, tumor necrosis factor.

4/3,K/22 (Item 5 from file: 149)

01814248 SUPPLIER NUMBER: 53587729 (USE FORMAT 7 OR 9 FOR FULL TEXT)

Surgical Removal of Visceral Fat Reverses Hepatic Insulin Resistance.

Barzilai, Nir; Li, She; Bing-Qian, Liu; Vuguin, Patricia; Cohen, Pinchas; Wang, Jiali; Rossetti, Luciano

Diabetes, 48, 1, 94(1)
Jan,
1999
PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0012-1797

LANGUAGE: English RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 4698 LINE COUNT: 00414

... the Animal Care and Use Committee of the Albert Einstein College of Medicine.

Preparation of total RNA from liver and fat depots and reverse transcriptase-*polymerase* chain reaction. Total hepatic RNA was prepared from frozen tissues using TRIzol reagent (GIBCO BRL, Gaithersburg, MD) as previously described (25). Total RNA from fat...

...g total RNA in 20 (micro)l final incubation volume by using SuperScript Preamplification System for First Strand cDNA Synthesis (GIBCO BRL) with random primer. *Polymerase* chain reaction (PCR) was carried out in a 50-(micro)l reaction mixture containing 4 (micro)l of the above first-strand cDNA, 5 (micro dNTP mix, 4 pmol of each primer, and 2.5 U Taq DNA *polymerase* (GIBCO BRL). For Glc-6-Pase, the sequence of upstream primer is AGG TGA GCC GCA AGG TAG ATC C; downstream primer, TGT CTT GGT...A 56:247-254, 1966

(8.) Hotamisligil GS, Peraldi P, Budavari A, Ellis R, While ME Spiegelman BM: IRS-1-mediated inhibition of insulin receptor *tyrosine* kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 271:665-668, 1996

(9.) Argaud D, Zhang Q, Pan w, Maitra S, Pilkis...

...growth factor-binding protein-1 gene expression through a conserved insulin response sequence. J Biol Chem 273:6482-6487, 1998

(14.) Mogul HR, Marshall M, *Frey* M, Burke HB, Wynn PS, Wilker S, Southern AL, Gambert SR: Insulin like growth factor-binding protein-1 as a marker for hyperinsulinemia in obese...acid; FM, fat mass; Glc-6-Pase, glucose-6-phosphatase; GP, glucose production; IGFBP, insulin-like growth factor binding protein; LBM, lean body mass; PCR, *polymerase* chain reaction; Peri, perinephric; RT, reverse transcriptase; TBS, Tris-buffered saline; TNF, tumor necrosis factor; VF, visceral fat.

4/3,K/23 (Item 6 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01697310 SUPPLIER NUMBER: 19475042 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Development of autoimmune diabetes in NOD mice is associated with the formation of peroxynitrite in pancreatic islet beta-cells.
Suarez-Pinzon, Wilma L.; Szabo, Csaba; Rabinovitch, Alex
Diabetes, v46, n5, p907(5)
May,
1997
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 4334 LINE COUNT: 00378

... isotype matched antibody (IgG, Cedarlane), 10 (micro)a/ml; and a mixture of anti-NT antibody (10 pa/ml, final concentration) and 3-nitro-L-*tyrosine* (Aldrich Chemicals, Milwaukee, WI) (10 mmol/l, final concentration) in 0.1 mol/l PBS to neutralize the anti-NT antibody. The cells were then...oxide (11,12). Peroxynitrite was detected in the islet cells by using immunohistochemical techniques and an antibody to NT, a specific marker for nitration of *tyrosine* residues on proteins by peroxynitrite (22). Furthermore, we found a marked increase in NT-expressing (Beta)-cells in NOD mice in association with (Beta)-cell... ...BALB/c mice, which do not develop diabetes (only 2% of (Beta)-cells were (NT.sup.+)). Because NT is produced by peroxynitrite-induced nitration of *tyrosine* residues on proteins (22), our findings imply that peroxynitrite-induced protein damage is occurring in the majority of (Beta)-cells at the onset of diabetes...ischemia-reperfusion injury. FEBS Lett 372:229-232, 1995

(16.) Miller MJ, Thompson JH, Zhang XJ, Sadowska-Krowicka H, Kakkis JL, Munshi UK, Sandoval M, *Rossi* JL, Eloby-Childress S, Beckman JS, Ye

YZ, Rodi CP, Manning P, Currie M, Clark DA: Role of inducible nitric oxide synthase expression and peroxynitrite...

...R2D6. J Clin Invest 74:25-38, 1984
(22.) Ischiropoulos H, Zhu L, Chen J, Tsai M, Martin JC, Smith CD, Beckman JS: Peroxynitrite-mediated *tyrosine* nitration catalyzed by superoxide dismutase. Arch Biochem Biophys 298:431-437, 1992
(23.) Rabinovitch A, Suarez-Pinzon WL, Sorensen O, Bleackley RC, Power RF: IFN...533, 1994
(29.) Heller B, Wang ZQ, Wagner EF, Radons J, Burkle A Febsel K, Burkart V, Kolb H: Inactivation of the poly (ADP-ribose) *polymerase* gene affects oxygen radical and nitric oxide toxicity in isles cells. J Biol Chem 270:11176 11180, 1995
From the Department of Medicine (W.L...

4/3,K/24 (Item 7 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01646857 SUPPLIER NUMBER: 18784870 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Predictors of thyroid tumor aggressiveness.
Clark, Orlo H.
The Western Journal of Medicine, v165, n3, p131(8)
Sep,
1996
PUBLICATION FORMAT: Magazine/Journal ISSN: 0093-0415 LANGUAGE: English
RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE: Professional
WORD COUNT: 6064 LINE COUNT: 00531

... ptc oncogene was found on chromosome 10q11-12 in the same region as that for multiple endocrine neoplasm type 2A.(53) The ptc oncogene has *tyrosine* kinase activity. This signal transduction pathway has been reported to be involved in the pathogenesis of papillary thyroid cancer.(53)
The p53 gene acts as...

...carcinomas(40) end in thyroid cancer cell lines.(41) Subsequent studies using single-strand conformation polymorphism analysis of complementary DNA fragments amplified by reverse transcriptase *polymerase* chain reaction documented the presence of mutations in exons 5, 6, 7, and 8 of the p53 gene in 12 of 49 thyroid carcinomas, but...Cooperative Group. Eur J Cancer 1979; 15:1033-1041 (20.) Hay ID: Prognostic factors in thyroid carcinoma. Thyroid Today 1989; 12:1 (21.) Cady B, *Rossi* R: An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery 1988; 104:947-953 (22.) Hay ID, Bergstralh EJ, Goellner JR, Ebersold...iodine therapy for apparently localized thyroid carcinoma--A decision analytic perspective. Endocrinol Metab Clin North Am 1990; 19:741-760 (68.) Cady B, Cohn K, *Rossi* RL, a al: The effect of thyroid hormone administration upon survival in patients with differentiated thyroid carcinoma. Surgery 1983; 94:978-983 (69.) Crile G...

4/3,K/25 (Item 8 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01616300 SUPPLIER NUMBER: 18114959 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Biology and treatment of adult acute lymphoblastic leukemia. (review article)
Levitt, Lee; Lin, Richard
The Western Journal of Medicine, v164, n2, p143(13)
Feb,
1996
PUBLICATION FORMAT: Magazine/Journal ISSN: 0093-0415 LANGUAGE: English
RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE: Professional
WORD COUNT: 11853 LINE COUNT: 01052

... genes with the minor BCR break point express a chimeric 7.0-kb messenger RNA and a p190 fusion protein. Both fusion proteins exhibit deregulated *tyrosine* kinase activity.[24,25] Chronic myeloid leukemia has been induced in some transgenic mice expressing p210, and acute leukemia has been seen in some transgenic mice expressing p190.[26,27]

The *polymerase* chain reaction (PCR) has recently been used to look for BCR-abl rearrangements: BCR-abl transcripts were found in 43% of adults with ALL, but...1988; 319:990-998 [24.] Konopka JB, Watanabe SM, Witte ON: An alteration of the human c-abl protein in K562 leukemia cells unmasks associated *tyrosine* kinase activity. Cell 1984; 37:1035-1042 [25.] Kurzrock R, Shtalrid M, Romero P, et al: A novel c-abl protein product in Philadelphia-positive...

...1990; 344: 251-253 [28.] Maurer J, Janssen JW, Thiel E, et al: Detection of chimeric BCR-ABL genes in acute lymphoblastic leukaemia by the *polymerase* chain reaction. Lancet 1991; 337:1055-1058 [29.] Klein G: Specific chromosomal translocations and the genesis of B-cell-derived tumors in mice and men...inversion in a T-cell lymphoma is caused by site-specific recombination between immunoglobulin and T-cell receptor loci. Nature 1986; 320:549-551 [50.] *Rossi* JF, Bataille R, Chappard D, Alexandre C, Janbon C: B cell malignancies presenting with unusual bone involvement and mimicking multiple myeloma - Study of nine cases... lymphoblastic leukemia. Blood 1986; 67:835-838 [75.] Miyamura K, Tanimoto M, Morishima Y, et al: Detection of Philadelphia chromosome-positive acute lymphoblastic leukemia by *polymerase* chain reaction: Possible eradication of minimal residual disease by marrow transplantation. Blood 1992; 79:1366-1370 [76.] Hughes TP, Morgan GJ, Martiat P, Goldman JM: Detection of residual leukemia after bone marrow transplant for chronic myeloid leukemia: Role of *polymerase* chain reaction in predicting relapse. Blood 1991; 77:874-878 [77.] Yamada M, Hudson S, Tournay O, et al: Detection of minimal disease in hematopoietic...
...Linke B, Bertram J, Rothaupt D, Hiddemann W: Characterization of clone-specific rearranged T-cell receptor [gamma]-chain genes in lymphomas and leukemias by the *polymerase* chain reaction and DNA sequencing. Blood 1994; 84:574-581 [80.] Hess CE, Zirkle JW: Results of induction therapy with vincristine and prednisone alone in...

4/3,K/26 (Item 9 from file: 149)

01521572 SUPPLIER NUMBER: 16942008 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Calcium signaling in neurons: molecular mechanisms and cellular consequences.(Signal Transduction)
Ghosh, Anirvan; Greenberg, Michael E.
Science, v268, n5208, p239(9)
April 14,
1995
PUBLICATION FORMAT: Magazine/Journal ISSN: 0036-8075 LANGUAGE: English
RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE: Academic
WORD COUNT: 10268 LINE COUNT: 00842

... is directly phosphorylated by PKC in neuronal cell cultures (17). Recent evidence suggests that voltage-sensitive ion channels and NMDArS can also be regulated by *tyrosine* phosphorylation (18). This is of interest not only from the perspective of channel modulation, but also because *tyrosine* phosphorylation may allow these channel proteins to influence intracellular signaling through direct intermolecular interactions. A central mechanism in the propagation of intracellular signals in response to receptor *tyrosine* kinase activation is the interaction of phosphorylated *tyrosine* residues on the receptor with SH2 domain--containing signaling molecules (19). The identification of SH2 domain--containing proteins that can interact with phosphorylated channel proteins...signaling pathway is activated by increases in intracellular [Ca.sup.2+] (50). This pathway has been extensively studied in the context

of signaling by receptor *tyrosine* kinases (19). Once activated, Ras appears to associate with and activate the serine-threonine kinase Raf, followed by the activation of a cascade of phosphorylation receptor *tyrosine* kinase activation interacts indirectly with the activated growth factor receptor via the adaptor protein Grb-2. This interaction is believed to then localize SOS to...

...mutation does not influence CREB stability, dimer formation, or binding to DNA, it is thought that phosphorylation at this site promotes the assembly of the *polymerase* II transcription complex at the TATA box and leads to the initiation of transcription. Recently two CREB-binding proteins, CBP and p300, have been characterized that may mediate the interaction of [Ser.sup.133]-phosphorylated CREB with the *polymerase* II transcription machinery (58). For example, CBP interacts specifically with CREB only after it is phosphorylated at [Ser.sup.133], and in cotransfection experiments CBP...of the synapse have also been shown to be regulated by neuronal activity (66). For example, the activation of VSCCs leads to the induction of *tyrosine* hydroxylase and the neuropeptide vasoactive intestinal peptide (VIP) in peripheral ganglia. Several synaptic vesicle-associated proteins are also induced by the activation of [Ca.sup ...Wayman, Z. Wu, D. R. Storm, Mol. Cell. Biol. 14, 8272 (1994); G. A. Wayman et al., J. Biol. Chem. 269,25400 (1994). (47.) U. *Frey*, Y.-Y. Huang, E. R. Kandel, Science 260, 1661 (1993); P. V. Nguyen, T. Abel, E. R. Kandel, ibid. 265, 1104 (1994); A. J. Cole...

...W. Saffen, J. M. Baraban, P. F. Worley, Nature 340, 474 (1989); P. K. Stanton and J. M. Sarvey, J. Neurosci. 4, 3080 (1984); U. *Frey* et al., Brain Res. 452, 57 (1988). (48.) P. Goelet, V. F. Castellucci, S. Schacher, E. R. Kandel, Nature 322, 419 (1986). (49.) R. P...

4/3,K/27 (Item 10 from file: 149)

01476984 SUPPLIER NUMBER: 14975326 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Mutational analysis of the NH2-terminal glycosylation sites of the insulin receptor alpha-subunit.
Caro, L. Heleen P.; Ohali, Anat; Gorden, Phillip; Collier, Elaine
Diabetes, v43, n2, p240(7)
Feb,
1994
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 3509 LINE COUNT: 00381

... contains the insulin-binding site. The [beta]-subunit consists of a short extracellular domain, a single transmembrane domain, and a cytoplasmic domain that is a *tyrosine* kinase. The receptor is known to contain covalently bound fatty acids [5], O-linked oligosaccharides [6], and N-linked oligosaccharides [7]. There are fourteen potential...

...or the second site, the first or the second site of the mutant EcoRV-Xho I segment was mutated back to normal by use of *polymerase* chain reaction (PCR) with normal primers [10,11] and then used in the triple ligation. The 3 site mutations were produced by ligating either of...as the WT receptor. The receptor from the [alpha]34 clone showed decreased autophosphorylation. Thus, the function of the receptor, at least as concerns the *tyrosine* kinase, appears to be normal. If the receptor is expressed at the cell surface, it binds insulin normally and stimulates autophosphorylation normally.

DISCUSSION

N-linked...Coussens L, Liao Y-C, Tsubokawa M, Mason A, Seeburg PH, Grunfeld C, Rosen OM, Ramachandran J: Human insulin receptor and its relationship to the *tyrosine* kinase family of oncogenes. Nature 313:756-61, 1985

[3.] Ebina Y, Ellis L, Jarnagin K, Edery M, Graf L, Clauser E, Ou J-H

...

...fragments: study of protein and DNA interactions. Nucleic Acids Res 16:7351-67, 1988

[11.] Kadowaki H, Kadowaki T, Wondisford FE, Taylor SI: Use of *polymerase* chain reaction catalyzed by Taq DNA *polymerase* for site-specific mutagenesis. Gene 76:161-66, 1989

[12.] Cama A, Marcus-Samuels B, Taylor SI: Immunological abnormalities in insulin receptors on cultured EBV...

...ML, Taylor SI: Substitution of isoleucine for methionine at position 1153 in the [beta]-subunit of the human insulin receptor: a mutation that impairs receptor *tyrosine* kinase activity, receptor endocytosis, and insulin action. J Biol Chem 267:8383-89, 1992 [17.] Rosen OM, Chia GH, Fung C, Rubin CS: Tunicamycin-mediated...

...processing of the insulin receptor precursor in vivo and in vitro. J Biol Chem 263:12809-12, 1988

[24.] Leconte I, Auzan C, Debant A, *Rossi* B, Clauser E: N-linked oligosaccharide chains of the insulin receptor [beta]-subunit are essential for transmembrane signaling. J Biol Chem 267:17415-23, 1992...RNA splicing. Mol Endocrinol 4:235-44, 1990

[30.] Flores-Riveros JR, Sibley E, Kastelic T, Lane MD: Substrate Phosphorylation catalyzed by the insulin receptor *tyrosine* kinase: kinetic correlation to autophosphorylation of specific sites in the [beta]-subunit. J Biol Chem 264:21557-72, 1989

[31.] Shier P, Watt VM: Primary...

4/3,K/28 (Item 11 from file: 149)

01359212 SUPPLIER NUMBER: 12357551 (USE FORMAT 7 OR 9 FOR FULL TEXT)

NIDDM associated with mutation in *tyrosine* kinase domain of insulin receptor gene. (non-insulin-dependent diabetes mellitus)

Cocozza, Sergio; Porcellini, Antonio; Riccardi, Gabriele; Monticelli, Antonella; Condorelli, Gianluigi; Ferrara, Assiamira; Pianese, Luigi; Miele, Claudia; Capaldo, Brunella; Beguinot, Francesco; Varrone, Stelio

Diabetes, v41, n4, p521(6)
April,
1992
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 4361 LINE COUNT: 00348

NIDDM associated with mutation in *tyrosine* kinase domain of insulin receptor gene. (non-insulin-dependent diabetes mellitus)

TEXT:

A population of 103 patients with non-insulin-dependent diabetes mellitus (NIDDM) was screened for mutations in the *tyrosine* kinase domain of the insulin receptor gene. Patient genomic DNAs corresponding to exons 17-21 of the insulin receptor gene have been amplified by *polymerase* chain reaction and analyzed by denaturing gradient gel electrophoresis (DGGE). One patient was identified with an altered pattern of mobility of exon 20 in the...

... severe insulin resistance[8-16]. Whether the insulin receptor mutations also contribute to the etiology of the common forms of NIDDM is unclear. Because the *tyrosine* kinase activity of the insulin receptor is required for insulin signal transduction[17,18] we postulate that an abnormal structure of this domain is present...

...and contributing to insulin resistance.

In this study, we have devised an efficient technique for screening a population of NIDDM patients for mutations in the *tyrosine* kinase domain of the insulin receptor by combining *polymerase* chain reactor (PCR) and

denaturing gradient gel electrophoresis (DGGE). With this approach, one patient was identified exhibiting a mutated receptor kinase allele.

RESEARCH DESIGN AND...

...previously described procedures[19]. Amplifications of patient genomic DNAs by PCR were performed separately with five pairs of oligoprimers, one for each exon encoding the *tyrosine* kinase domain of the insulin receptor[20]. The oligoprimer sequences (S, sense; A, antisense) are as follows: exon 17 5'-CATGC TCTGTGTACGTGCCG-3' (S), 5...

...Mm KCl, 0.001% gelatin) containing 20 pmol of each oligonucleotide primer and 10 nmol of each DNA triphosphate. One unit of thermus aquaticus DNA *polymerase* (Perkin-Elmer/Cetus, Norwalk, CT) was added, and 100 [mu]l mineral oil was layered on the samples. Samples were then incubated at 95 [degrees...

...10 [mu] Ci (3.3 pmol) [alpha]-[[P.sup.32]]ATP (Amersham, Aylesbury, UK), and 2 [mu]l of 1.5 U/ [mu]l T7 *polymerase* were added. The labeling reaction (4.5 [mu]l) was directly transferred in four prewarmed tubes containing 2.5 [mu]l each of termination mix...7.6), 0.05% albumin in the absence or the presence of 1 [mu] M insulin (final vol 70 [mu]l). The substrate poly Naglutamate, *tyrosine* (4:1) (final concn 2.5 mg/ml) [MgCl.sub.2] (final concn 20 mM) were added along with ATP (final concn 25 mM) and...

...the forearm flow measured by the dye technique[25].

RESULTS

Identification of receptor kinase mutations. DGGE mobility was used to screen for alterations in the *tyrosine* kinase domain corresponding exons 17-21 of the insulin receptor gene in 103 NIDDM patients. Alterations were observed in one patient, a 31-yr-old...

...substitution in codon 1152 (numbering system according to ref. 26), resulting in the replacement of Arg with Gln. No other mutation was detected in the *tyrosine* kinase domain of any of the alleles of the insulin receptor gene in the proband. The mutation was inherited from the father, who was also...a pivotal role in the cellular responsiveness to insulin and resistance of the cells to insulin action is a prominent feature of NIDDM[7]. The *tyrosine* kinase activity of the receptor is required for insulin action[6], leading to the hypothesis that abnormalities in this domain of the molecule may contribute...

...these studies to small samples of patients, and thus it is unclear whether receptor mutations contribute to NIDDM etiology. To identify genetic alterations in the *tyrosine* kinase domain of the insulin receptor, we used DGGE, which is a gel system that separates DNA fragments according to their melting properties[4]. With...

...among 103 NIDDM patients, we found one subject exhibiting a single point mutation at codon 1152 leading to a Glu for Arg substitution in the *tyrosine* kinase domain to the receptor sequence.

Because DGGE is unable to detect mutations in the primers' matching sequences, only 658 of 776 bp (84%) coding...

...heterozygous for the mutation. It is possible that the [Gln.sup.1152] substitution impaired the insulin-induced receptor internalization and that the receptors with inactive *tyrosine* kinase accumulated at the cell surface. However, it is also possible that mutated receptors inhibited the kinase activity of the normal receptors, which was the...RK, Gelfand DH, Stoffel S, Scharf SJ, Higuchi R, Horn GY, Mullis KB, Erlich HA: Primer-directed enzymatic amplification of DNA with a thermostable DNA *polymerase*. Science 239:487-91, 1988 [4.] Myers RM, Maniatis T, Lerman LS: Detection and localization of single base changes by denaturing gradient gel electrophoresis. Methods...

...VC, Cox DR, Lerman LS, Myers RM: Attachment of a 40-base-pair G + C-rich sequence (GC-clamp) to genomic DNA fragments by the *polymerase* chain

reaction results in improved detection of single-base changes. Proc Natl Acad Sci USA 86:232-36, 1989 [6.] Rosen OM: Afther insulin binding...

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...1398-406, 1988 [30.] Sbraccia P, Goodman PA, Maddux BA, Wong KY, Chen Y-Dl, Reaven GM, Goldfine ID: Production of inhibitor of insulin-receptor *tyrosine* kinase in fibroblasts from patient with insulin resistance and NIDDM. Diabetes 40:295-99, 1991 [31.] Debant A, Clauser E, Ponzio G, Filloux C, Auzan C, Contreres JO, *Rossi* B: Replacement of insulin receptor *tyrosine* residues 1162 and 1163 does not alter the mitogenic effect of hormone. Proc Natl Acad Sci USA 85:8032-36, 1988

...DESCRIPTORS: Protein-*Tyrosine* Kinase...

4/3,K/29 (Item 12 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01099266 SUPPLIER NUMBER: 04163484 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Gordon Research Conferences. (Summer, 1986)
Cruickshank, Alexander M.
Science, v231, p1163(37)
March 7,
1986
PUBLICATION FORMAT: Magazine/Journal ISSN: 0036-8075 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Academic
WORD COUNT: 28553 LINE COUNT: 03203

... with G3PDH"; E. Miles, "Properties and mechanisms of trytophan synthetase." Phosphothioates (G. L. Kenyon, chairman): F. Eckstein, "Interactions of nucleases with phosphoth ioate DNA"; P. *Frey*, "Newer studies of phosphorothiates and phosphotransferases."

3 July. Membranes and related systems: M. Tsai (subject to be announced): B. Hess, "Protonation studies of bacterial rhodopsin...in plants and their role in evolution"; Charles S. Levings III, "Interesting plant mitochondrial genes"; Michael Little, "Characterization and expression of chloroplast genes for RNA *polymerase* subunits."

18 July. (Kenneth N. Timmis, discussion leader): A. M. Chakrabarty, "Plasmid encoding degradation of synthetic halogenated compounds"; K. Brooks Low, "Single-stranded DNA binding...function"; Ranjan Sen, "Immunoglobulin gene trans-acting factor." Insulin action (T. Gelehrter, discussion leader): Harvey Lodish, "Molecular biology of the glucose transporter"; Ron Kahn, "Tyrosine *kinase* and insulin action"; Ora Rosen,

"Insulin receptor-structure function."
5 August. Hormones and gene expression (B. O'Malley, discussion leader): Robert Roeder, "Eucaryotic transcription factors...of mismatch repair."
3 July. DNA polymerization (D. Korn, session chairman): T. Wang, "Polymerasealpha: Gene localization and conservation"; S. Wilson, "Cloning of mammlian DNA polymerase-*B*"; T. Kunkel, "Fidelity of eucaryotic DNA polymerases." Genomic evolution (R. Haynes, session chairman): W.F. Doolittle, "Origin and evolution of introns."
4 July. Late breaking...phosphodiesterases"; J. H. Wang, "Regulation by cascade mechanisms"; R. Davis, "Drosophila dunce genes." (E. G. Krebs, discussion leader): B. Sefton, "Cellular and oncogene tyrosine kinases"; *E*. J. Neer, "Brain tyrosine kinases"; *M*. A. Simon, "Expression of c-src in Drosophila."
25 June. (J. Heller-Brown, discussion leader): J. Heller-Brown, "GTP-dependent inositol-P formation"; R. Michell...

4/3,K/30 (Item 1 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00124247

Frequency of Major Molecular Responses to Imatinib or Interferon Alfa plus Cytarabine in Newly Diagnosed Chronic Myeloid Leukemia (Original Articles)

Hughes, Tim P.; Kaeda, Jaspal; Branford, Susan; Rudzki, Zbigniew; Hochhaus, Andreas; Hensley, Martee L.; Gathmann, Insa; Bolton, Ann E.; van Hoomissen, Iris C.; Goldman, John M.; Radich, Jerald P.; for the International Randomised Study of Interferon versus STI571 (IRIS) Study Group.
The New England Journal of Medicine
Oct 9, 2003; 349 (15),pp 1423-1432
LINE COUNT: 00495 WORD COUNT: 06837

...of all patients in this trial who had a complete cytogenetic remission.
Methods: Levels of BCR-ABL transcripts were measured by a quantitative real-time *polymerase*-chain-reaction assay. Results were expressed relative to the median level of BCR-ABL transcripts in the blood of 30 patients with untreated CML in...

TEXT
...t(9;22)(q34;q11), forms the Philadelphia chromosome (Ph) and creates a novel fusion gene, BCR-ABL. (Ref. 1) This gene expresses an activated *tyrosine* kinase that is central to the pathogenesis of CML. (Ref. 2,3) The median survival among patients with CML is three to six years, with...

...Ref. 7,8) The development of accurate techniques to measure the BCR-ABL transcripts in peripheral blood or bone marrow by a quantitative reverse-transcriptase *polymerase* chain reaction (PCR) has allowed patients in complete cytogenetic remission to be stratified further. (Ref. 9-16) The level of BCR-ABL transcripts can predict...

...Imatinib mesylate (Gleevec, Novartis) is a *tyrosine* kinase inhibitor that blocks the kinase activity of BCR-ABL, thus inhibiting the proliferation of Ph-positive progenitors. (Ref. 19,20) Imatinib has shown activity...

...Table 1.-Base-Line Characteristics of All Patients Who Had a Complete Cytogenetic Remission and of All Patients Who Had a Complete Cytogenetic Remission and *Polymerase*-Chain-Reaction (PCR) Data Available *.**TABLE OMITTED**
Levels of BCR-ABL Transcripts at the Time of a Complete Cytogenetic Remission

At the time of a...

...128Patients Who Were Treated with Imatinib for 12 Months without a Complete Cytogenetic Remission and 240 Patients Who Had a Complete Cytogenetic Remission and Had *Polymerase*-Chain-Reaction Data Available, According to the Extent of the Reduction from Base Line in BCR-ABL Transcript Levels.P<0.001 for the overall...

...G. Saglio (Orbassano), R. Fanin (Udine), G. Rosti (Bologna), F. Mandelli (Rome), E. Morra (Milan), A. Carella (Genoa), M. Lazzarino (Pavia), M. Petrini (Pisa), P. *Rossi* Ferrini (Florence), F. Nobile (Reggio Calabria), V. Liso (Bari), F. Ferrara (Naples), V. Rizzoli (Parma), G. Fioritoni (Pescara), G. Martinelli (Milan); the Netherlands -- J. Cornelissen...

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...cessation of interferon-(alpha). J Clin Oncol 2002;20:214-20.
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...9:329-35.
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...disease are associated with continuing remission. Blood 2000;95:62-6.
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...9.
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...transcript numbers in chronic myeloid leukemia patients who relapse

after bone marrow transplantation. Blood 1996;87:4473-8.
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...Suppl 3:62-8.
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4/3,K/31 (Item 2 from file: 444)

DIALOG(R)File 444:New England Journal of Med.

00121741

Advances in Immunology: Immunomodulation of Autoimmune and Inflammatory Diseases with Intravenous Immune Globulin (Review Article)

Kazatchkine, Michel D.; Kaveri, Srini V.
The New England Journal of Medicine
Sep 6, 2001; 345 (10),pp 747-755
LINE COUNT: 00433 WORD COUNT: 05982

TEXT

...of immune globulin begins with donor selection and screening of plasma donations for hepatitis C virus, hepatitis B virus, HIV, and hepatitis B surface antigen. *Polymerase*-chain-reaction testing of samples of individual plasma donations or pooled plasma has recently been introduced. There has been no report of the transmission of...

...structures in the extracytoplasmic region represent immunoglobulin-like domains. Individual subunits of Fc receptors in the intracytoplasmic region are labeled (alpha) and (gamma). The immunoreceptor *tyrosine*-based activation motifs are depicted as blue bands, and the immunoreceptor *tyrosine*-based inhibition motif of Fc(gamma) receptor RIIB is depicted by the pink circle. Fc(gamma) RIII receptors ...We are indebted to D. Baruch, B. Bellon, A. Coutinho, M.H. Jouvin, S. Lacroix-Desmazes, J.C. Mani (deceased), A. Pashov, N. Prasad, F. *Rossi*, G. Ruberti, Sooryanarayana, S. Spalter, Y. Sultan, and T. Vassilev for their help with some of the work reviewed here; and to E. Sercarz for...

CITED REFERENCES

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Maisonneuve P, Nydegger UE. Anti-idiotypic suppression of autoantibodies to factor VIII (antihaemophilic factor) by high-dose

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4/3,K/32 (Item 3 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00119597

A Population-Based Study of the Clinical Expression of the Hemochromatosis Gene (Original Articles)

Olynyk, John K.; Cullen, Digby J.; Aquilia, Sina; Rossi, Enrico; Summerville, Lesa; Powell, Lawrie W.
The New England Journal of Medicine
Sep 2, 1999; 341 (10),pp 718-724
LINE COUNT: 00357 WORD COUNT: 04936

TEXT
...was identified on chromosome 6. (Ref. 5) A single mutation (G to A at nucleotide 845) in the HFE gene results in the substitution of *tyrosine* for cysteine at amino acid 282 and is termed the C282Y mutation. A second mutation (C to G at nucleotide 187) in the HFE gene...

...at amino acid 63 and is termed the H63D mutation. These mutations are usually detected by restriction-enzyme digestion after amplification of DNA with the *polymerase* chain reaction (PCR). The C282Y mutation results in the formation of a unique SnaBI restriction site, whereas the H63D mutation results in the loss of...

CITED REFERENCES
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15. Bacon BR...

4/3,K/33 (Item 4 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00115359

Gastric Carcinoma (Correspondence)

Lowy, Andrew M.; Mansfield, Paul F.; Greene, Frederick L.; Kullmann, Frank; McClelland, Michael; Fuchs, Charles S.; Mayer, Robert J.
The New England Journal of Medicine
Nov 23, 1995; 333 (21),pp 1426-1428
LINE COUNT: 00121 WORD COUNT: 01681

TEXT
In addition, the authors mention some growth factors but neglect others. For example, the K-sam gene, which encodes a *tyrosine* kinase receptor belonging to the fibroblast growth-factor receptor and is amplified preferentially in poorly differentiated adenocarcinoma or scirrhous carcinoma, is mentioned. On the other...

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Reference 012
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4/3,K/34 (Item 5 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00114617

Childhood Leukemias (Review Article)

Pui, Ching-Hon.
The New England Journal of Medicine
Jun 15, 1995; 332 (24),pp 1618-1630
LINE COUNT: 00632 WORD COUNT: 08724

TEXT
...ALL with this rearrangement, the breakpoint within the BCR region is more centromeric, yielding a smaller (185 kd) chimeric protein. (Ref. 46) Both proteins are *tyrosine* kinases, but the 185-kd form has more potent transforming activity. (Ref. 47) Regardless of the type of BCR-ABL protein, blast cells with the...The *polymerase* chain reaction (PCR) has been tested extensively as a method of amplifying RNA or DNA sequences unique to the malignant clone, including fusion-gene transcripts...

CITED REFERENCES
...bcr gene by 9;22 breakpoints in pediatric acute leukemias. Blood 1991;77:324-30.
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...Jr, Levine K, DeBlasio A, Frankel SR, Dmitrovsky E, Warrell RP Jr.

Detection of minimal residual disease in acute promyelocytic leukemia by a reverse transcription *polymerase* chain reaction assay for the PML/RAR-(alpha) fusion mRNA. Blood 1993;82:1689-94.

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4/3,K/35 (Item 6 from file: 444)

00114412

Medical Progress: Primary Sclerosing Cholangitis (Review Articles)

Lee, Young-Mee; Kaplan, Marshall M.
The New England Journal of Medicine
Apr 6, 1995; 332 (14),pp 924-933
LINE COUNT: 00615 WORD COUNT: 08495

TEXT

...on animals suggests a third possible cause of primary sclerosing cholangitis: bacterial products acting as toxic proinflammatory agents. N-formyl l-methionine l-leucine l-*tyrosine* is a peptide produced by enteric flora. When this peptide, labeled with iodine-125, was introduced into the colons of rats with experimentally induced colitis...

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